

SYNTHESIS OF SOME
3,5-DISUBSTITUTED TETRAHYDRO-2H-1,3,5-
THIADIAZINE-2-THIONE DERIVATIVES

A MASTER'S THESIS
in
CHEMISTRY
Middle East Technical University

by
Zerrin ZERENLER
September 1988

TO MY MOTHER

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Approval of the Graduate School of Natural and Applied
Sciences



Prof. Dr. Alpay ANKARA

Director

I certify that this thesis satisfies all the requirements as
a thesis for the degree of Master of Science in Chemistry

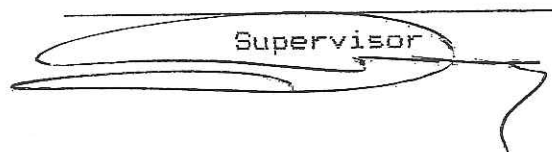


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ABSTRACT

SYNTHESIS OF SOME 3,5-DISUBSTITUTED TETRAHYDRO-2H-1,3,5- THIADIAZINE-2-THIONE DERIVATIVES

ZERENLER, Zerrin

M.S. in Chemistry

Supervisor: Prof. Dr. Okan TARHAN

September 1988

In this study, six different 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives were synthesized by addition of carbon disulfide, potassium hydroxide, formaldehyde and 8-hydroxy-5-aminomethyl quinoline to various primary amines.

These synthesized derivatives are expected to show antifungal effects. The antifungal, antiviral, and antibacterial properties of tetrahydro-2H-1,3,5-thiadiazine-2-thione are known for long time. On the other hand 8-hydroxy-5-aminomethyl quinoline was recently recognised for its antifungal activity. Combination of these two molecules is expected to show synergetic effect.

Key words: Antifungal, Synergetic, Thiadiazine

ÖZET

ÇEŞİTLİ 3,5-DİSUBSTİTÜE-TETRAHİDRO-2H-1,3,5-THİADİAZİNE- 2-TİON TÜREVLERİNİN SENTEZLENMESİ

ZERENLER, Zerrin

Yüksek Lisans Tezi, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Okan TARHAN

Eylül, 1988

Bu çalışmada çeşitli primary aminler kullanılarak buna karbon disülfür, potasyum hidroksit, formaldehit ve 8 hidroksil-5-aminometil quinolin ilavesi ile altı değişik 3,5-disubstitue-tetrahidro-2H-1,3,5-thiadiazin-2-tion türevleri sentezlenmiştir.

Çalışmamızda sentezlediğimiz türevlerin antifungal etki göstermesi beklenmektedir, Çünkü antifungal, antiviral, antibakteriyel özellikleri bilinen tetrahidro-2H-1,3,5-thiadiazin-2-tion molekülü ile, son yıllarda antifungal etkisi saptanan 8-hidroksil-5-aminometil quinolin molekülü birleştirilmiştir. Bu "synergetic" etkinin elde edilmesinde uygulanan klasik bir yöntemdir.

Anahtar Kelimeler: Antifungal, Synergetic, Thiadiazine

ACKNOWLEDGMENT

I wish to express my most sincere thanks and gratitude to my supervisor Prof.Dr.Okan Tarhan for his everending and skilfull guidance throughout the course of this work.

I am also greatly indebted to Prof.Dr.Mevlüt Ertan for his kind helps, valuable advice and criticism during the research..

I wish to extend my most profound thanks and love to my mother and to my fiance Mesut Çalışkan for their support, patience and understanding.

Finally I wish to thank Dr.Cihangir Tanyeli and all in Chemistry Department who have helped in building up of this thesis.

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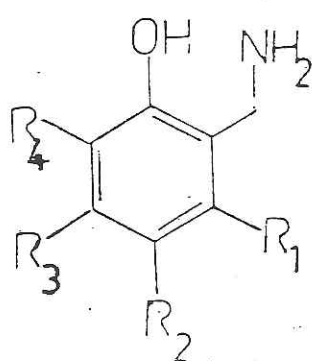
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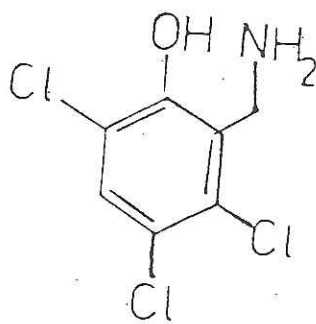
INTRODUCTION

Fungii is a very important group in botany because of their negative effects to the human life and agriculture. The studies on antifungal agents are being continued by some research centers. Some of the fungii are the cause of diseases on human beings, animals and plants. Therefore several dozen antifungal, antibacterial and antibiotic agents are used to prevent diseases both in plants and in humans, although some toxicity problems arise when consumption exceeds, certain limits. The importance of these agents and their effects push the scientists to the synthesis of new derivatives.

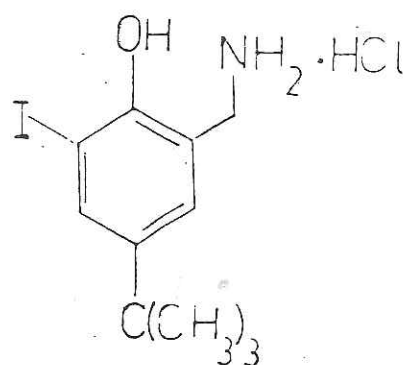
The aim of this work was to synthesize tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives which show antifungal activity on diseases caused by fungus. 8-hydroxy-5-amino methyl quinoline was used for the aminomethyl functionality whose antifungal activity has been established. In recent years, scientists have studied on 2-(aminomethyl)phenol and examined biological and chemical activities of this compound, by changing positions of hydroxyl and aminomethyl groups, they also pointed out that aminomethyl moiety is the most important group regarding the biological activity which is also affected by R_1 , R_2 , R_3 and R_4 substituents (1). For example compound (2) was tested in rats and dogs and showed saluretic and diuretic activity. But (3) was found to have antihypertensive and antiinflammatory properties [1].



(1)

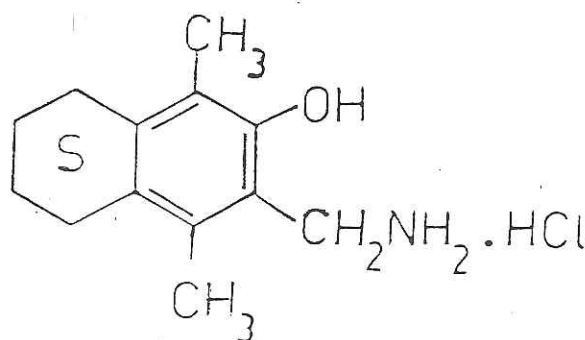


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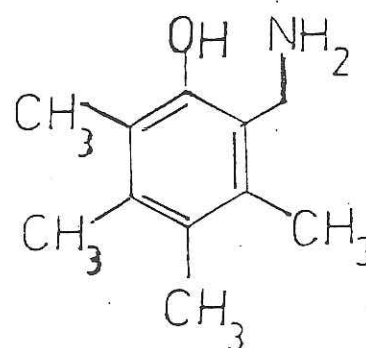


(3)

Chemical and biological activity of bicyclic ring fused 2-(aminomethyl)phenol have also been studied and compared with the structurally similar monocyclic ring. The results have shown that the carboxylic annulation at the 4,5 position and 5,6 position of the 2(aminomethyl)phenol increased the saluretic activity. According to these searches the potency of tetralin (4) is greater than that of the structurally similar monocyclic counterpart 2-(aminomethyl)-3,4,5,6-tetramethyl phenol (5) [2].



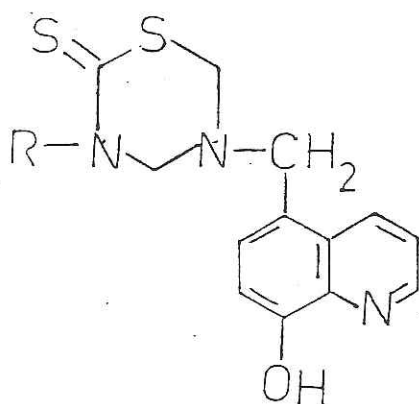
(4)



(5)

Scientists suggested that some quinoline derivatives which contain aminomethyl moiety show also biological and chemical activity. Antimalaria effect is one of them [3].

Although 8-hydroxy-quinoline methylamine has shown anti fungal activity, we have decided to combine 8-hydroxy-5-aminomethyl quinoline and tetrahydro thiadiazine, because of antifungal activity of 8-hydroxy-5-aminomethyl quinoline and well known fungicidal activity of tetrahydro thiadiazine (6).



(6)

II. CHEMICAL ASPECTS OF TETRAHYDRO-2H-1,3,5,-THIADIAZINE-2-THIONE

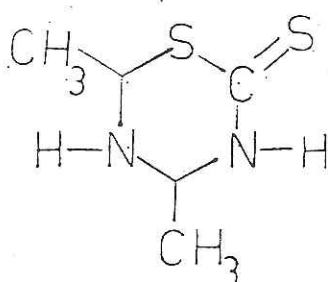
Although the reaction product of aldehydes with carbon disulfide and ammonia or primary amines have been known for nearly a century, none of the formula suggested for them is entirely satisfactory. The best known of the series, the reaction product of acetaldehyde, ammonia, and carbon disulfide, is "carbothialdine" which, despite its name, has not been shown to be related to the thialdines which are 1:3:5-dithiazines formed by the action of hydrogen sulfide on aldehyde ammonias.

It appears to be generally agreed that the reaction of aldehyde with carbon disulfide and primary amines or ammonia usually gives the same product as that obtained by reaction between the aldehyde and the dithiocarbamate. Levi has shown that 2 moles of aldehyde were involved in the reaction. He also showed that potassium dithiocarbamates did not react with aldehydes [4,5].

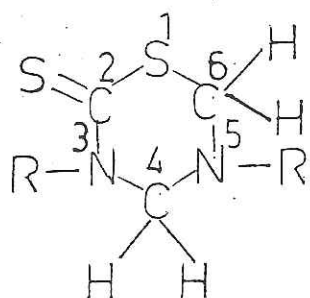
Carbothialdine ($C_5H_{10}N_2S_2$) has been prepared by the reaction of carbon disulfide with acetaldehyde ammonia by Redtenbacher and Liebig in 1848. However they erroneously identified the structure as 1,3,5,-dithiadiazines instead of 4,6-dimethyl-tetrahydro-1,3,5-thiadiazine-2-thione (7). Then following years, Guareschi, Muldur, Levi, Gimignani, Delepine have synthesized these types of compounds and new derivatives. But all studies including formation of

compounds and determination of their properties gave unsatisfactory results.

However absorption spectra were accord with the proposed formula. Depending on the absorption spectra, the correct structure (8) was given by Ainley in 1944 [6].



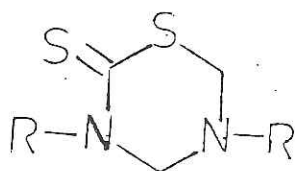
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(8)

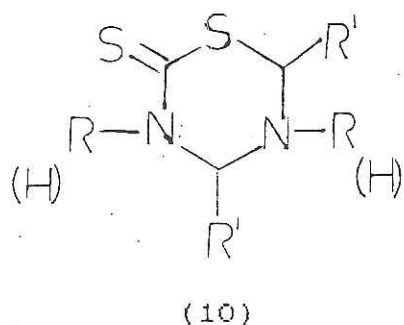
Tetrahydro-2H-1,3,5-thiadiazine-2-thione structure includes four groups of compound which are:

- i) 3,5-Disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione (9)

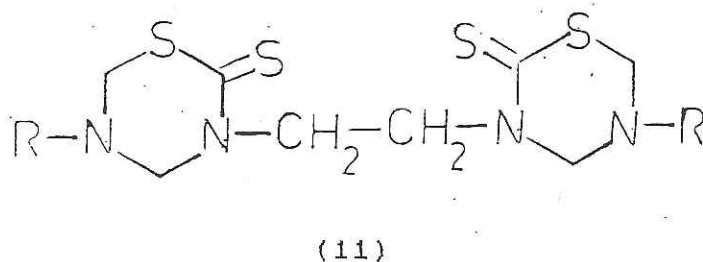


(9)

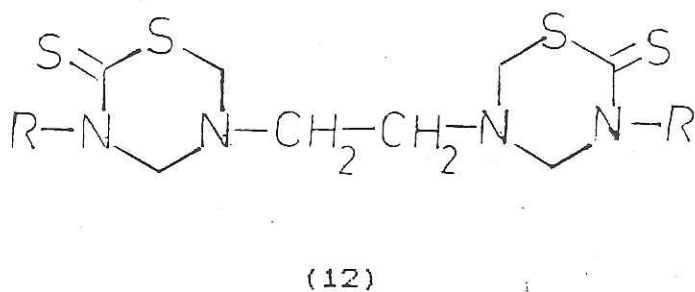
- ii) 4,6-Disubstituted or 3,4,5,6-tetrasubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione (10)



- iii) 3,3'-Ethylenebis-5,5'-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione (11)



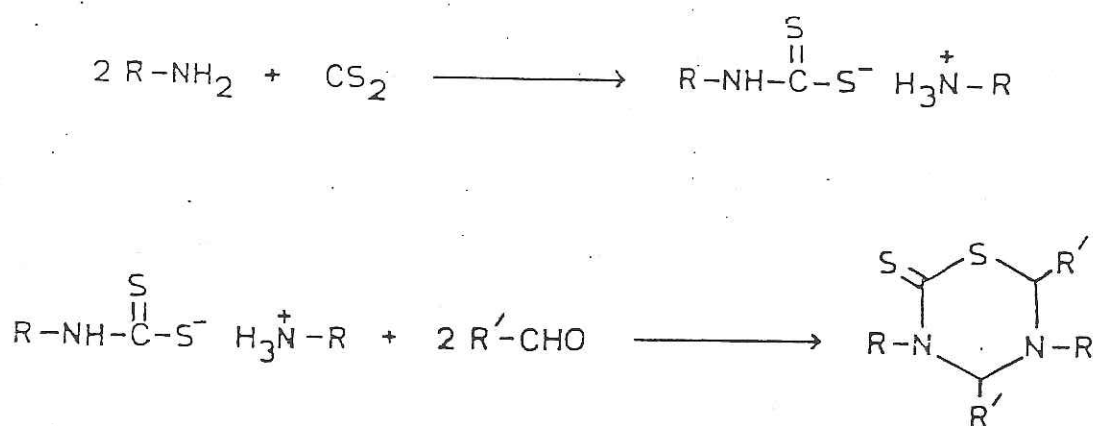
- iv) 5,5'-Ethylenebis-3,3'-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione (12)



2.2. Synthesis

2.2.1. Synthesis of the 4,6-Disubstituted Derivatives

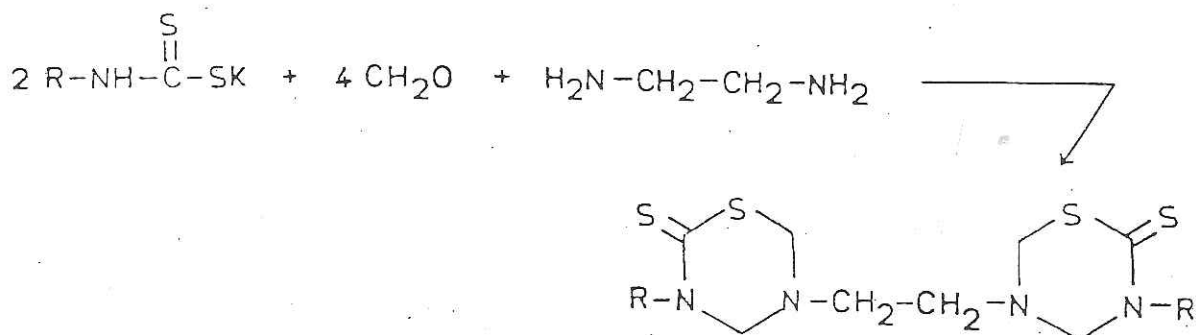
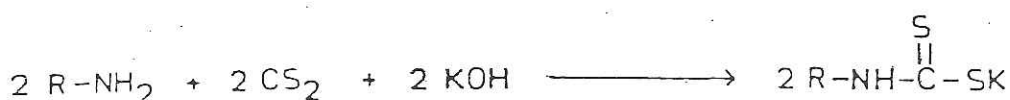
Wauffen, Shorr, Rieche and coworkers showed that the reaction occurred with the primary amine, carbon disulfide and formaldehyde in the presence of suitable solvent (Scheme 1) [7.8.9].



(Scheme 1)

2.2.2. Synthesis of the 5,5'-Ethylenebis-3,3'-Disubstituted Derivatives

Reaction of potassium dithiocarbamate with 4 moles of formaldehyde and 1 mole of ethylene diamine gives the 5,5'-Ethylenebis-3,3'-disubstituted derivative (Scheme 2) [9].

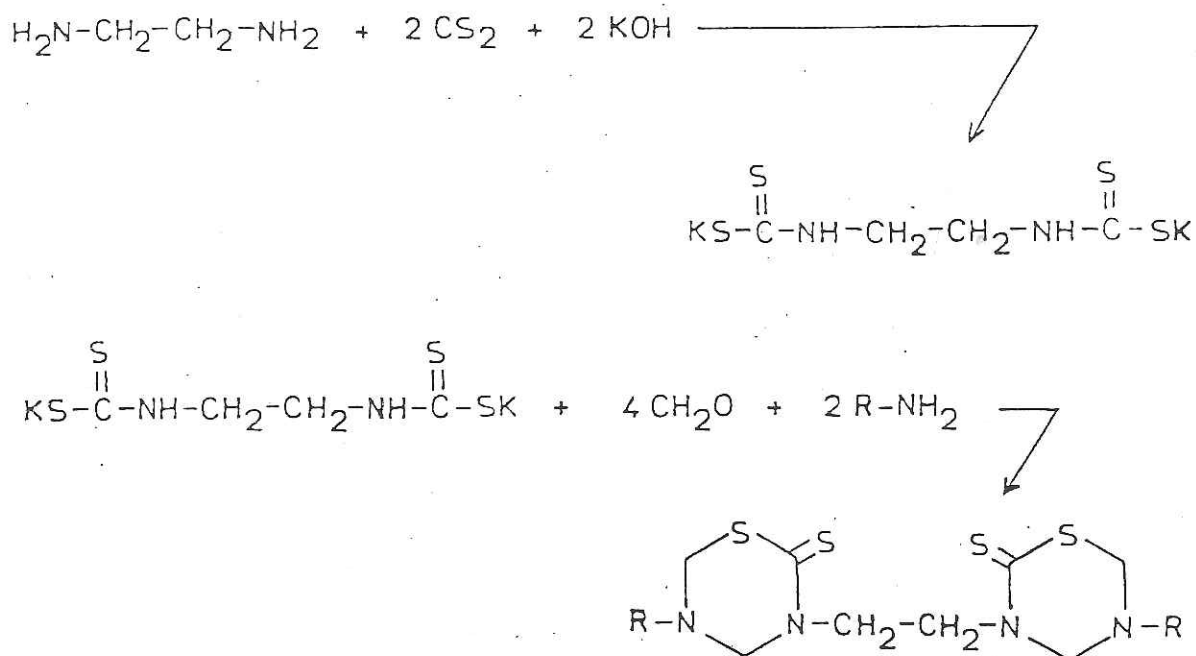


(Scheme 2)

2.2.3. Synthesis of the 3,3'-Ethylenebis-5,5'-Disubstituted Derivatives

Dipotassium ethylene bis dithiocarbamate was obtained from the reaction of 1 mole of ethylene diamine, 2 moles of carbon disulfide and 2 moles of potassium hydroxide. When dipotassium ethylene bis dithiocarbamate was treated with 4 moles of formaldehyde and 2 moles of primary amine, 3,3'-ethylene bis-5,5'-disubstitute derivatives could be obtained (Scheme 3) [7,9].

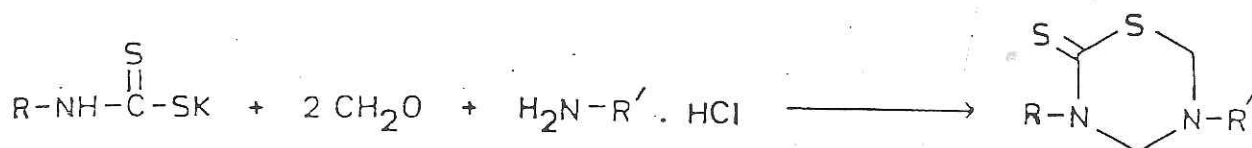
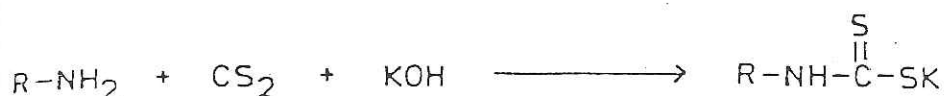
These types of derivatives can be obtained, when the product from the reaction between isothiocyanate solution in alcohol and equimolar amount of sodium bisulfide is treated with formaldehyde and amine chloride or sulphate salts.



(Scheme 3)

2.2.4. Synthesis of the 3,5-Disubstituted Derivatives

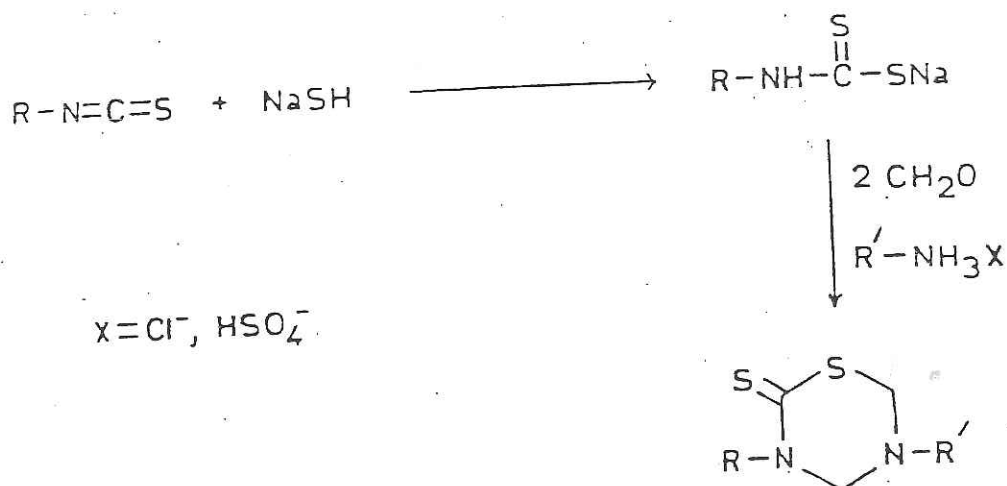
In order to synthesize the compounds which have different substituents on the third and fifth positions, primary amine was reacted with carbon disulfide and potassium hydroxide to afford the potassium dithiocarbamate. When this product was reacted with 2 moles of formaldehyde and 1 mole of different amine hydrochloride, target compounds were obtained (Scheme 4) [7,8,9,10].



(Scheme 4)

Traber used sodium carbonate as a base instead of KOH [11].

Different methods can be applied for the synthesis of 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives. These methods can be divided into two groups. In the first method the dithiocarbamate is obtained from the reaction between solutions of primary amines in different solvents and carbon disulfide in the presence of alkali metal salts. When this product is reacted with formaldehyde and primary amine, 3,5-disubstitute derivatives are obtained. In the second method, the product (Scheme 5) is obtained by treating isothiocyanites with equimolar sodium bisulfide in alcohol and then reacting it with formaldehyde and primary amine salts [12].



(Scheme 5)

In this work, first method was applied because of better yield and soft reaction condition over the second one.

2.2.5. Aim of the Work

The aim of this study is to prepare some derivatives of 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione (Table 1).

In our work, we have synthesized six new derivatives of 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione. 8-Hydroxy-5-aminomethyl quinoline was used because of its high fungicidal activity. When the product of 8-hydroxy-5-acetaminomethyl quinoline, which is obtained from the reaction between N,N'-methylene bis acetamide and 8-hydroxy quinoline, is hydrolyzed, 8-hydroxy-5-aminomethyl quinoline is isolated which has antifungal activity.

On the other hand 3,5-derivatives of tetrahydro-2H-1,3,5-thiadiazine-2-thione have aroused interest as fungicides with special use, particularly in the agriculture as soil fungicides, and these derivatives are known as potent antiviral, antifungal, antibacterial and nematocide compounds involved in different composition in drugs.

It has been decided to combine 8-hydroxy-5-amino methyl quinoline and tetrahydro thiadiazine, because of antifungal activity of 8-hydroxy-5-aminomethyl quinoline and well known fungicidal activity of tetrahydro thiadiazine.

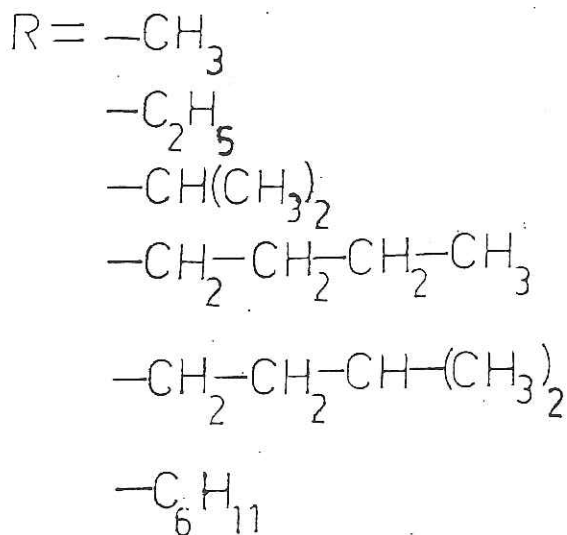
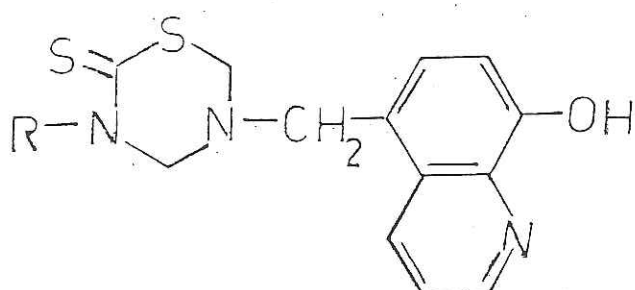
In the second step of this study, cyclization of tetrahydro-2H-1,3,5-thiadiazine-2-thione ring has been planned to be synthesized with different substitutions at 5th and 3rd positions such as; formaldehyde and primary amine which gives methyl amine, ethyl amine, isopropyl amine, isopentyl amine, n-butyl amine and cyclohexyl amine substituents have been placed at 3rd position, and 5-methyl-8-hydroxy-quinoline function at 5th position of parent compound.

In recent years some scientists suggested that the 3rd and 5th positions at 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione have an importance on their biological activities.

Amines are medically and biologically important

compounds, therefore the primary amines were used at the 3rd position. On the other hand 5-amino methyl-8-hydroxy quinoline has antifungal property. Therefore it was placed at the 5th position.

TABLE I



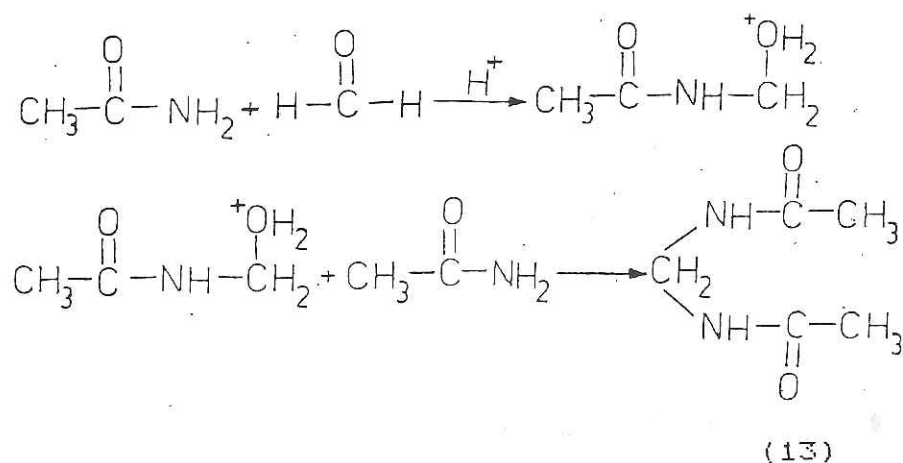
III. THEORY

3.1. Theory

Hydroxyl aminomethyl quinoline derivatives which were developed in recent years have been used for the kinds of antimicrobial drugs and a variety of useful antifungal agents. On the other hand, tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives are shown potent antiviral, antibacterial, insecticide, nematodes and antifungal activities in different compositions and drugs.

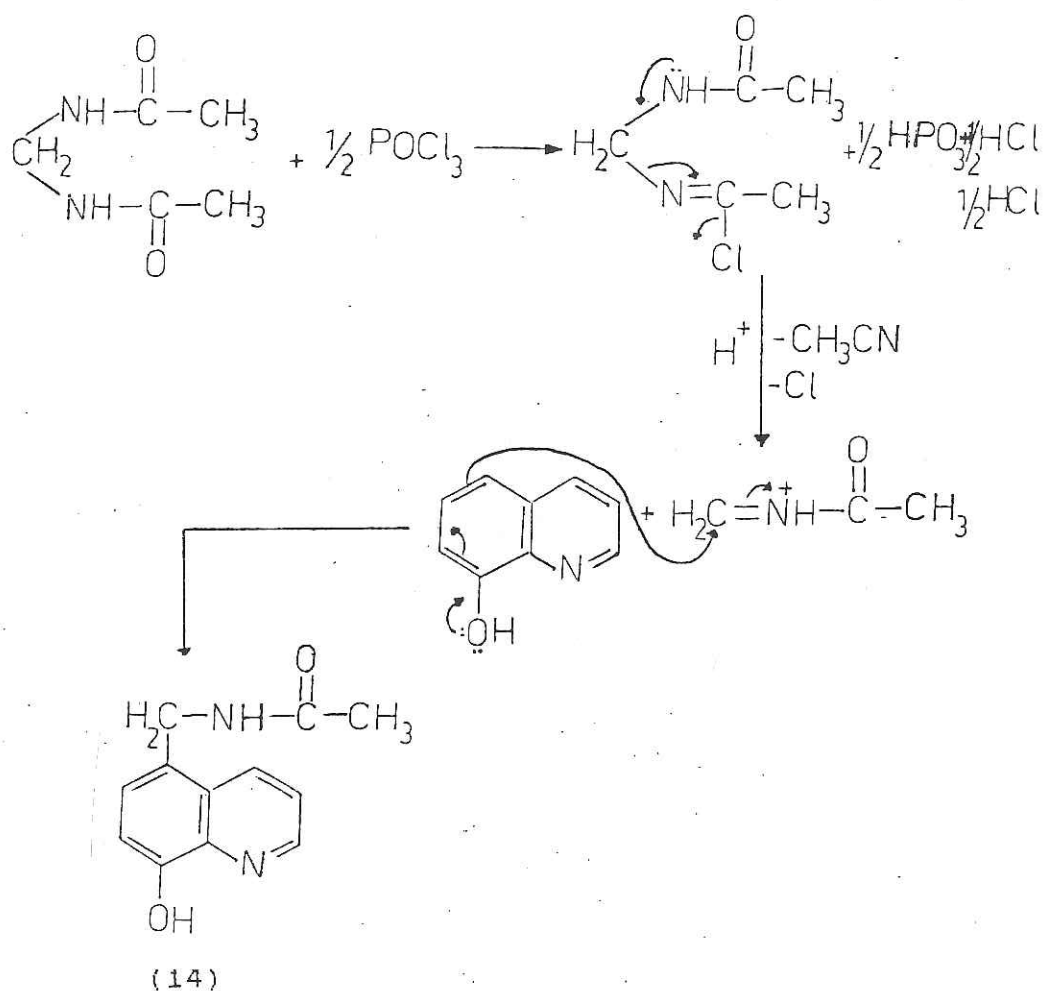
The syntheses of 8-hydroxy-5-aminomethyl quinoline could be obtained according to the following method:

Firstly N-N' methylenebis acetamid (13) was synthesized by the reaction of acetamide with paraformaldehyde in acidic medium (Scheme 6) [13].



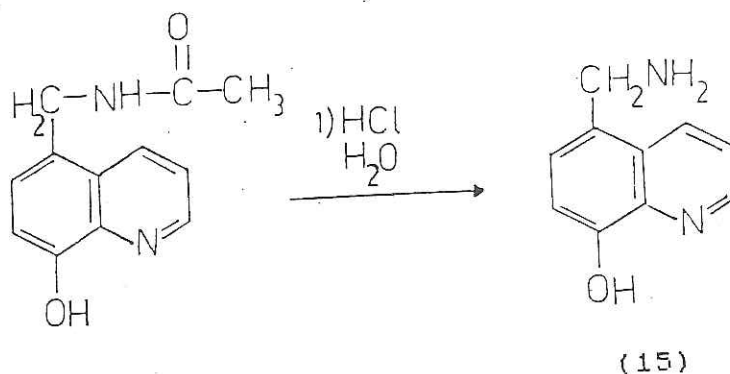
(Scheme 6)

Then the reaction of 1 mole of N-N'methylene bis acetamid, 1/2 mole of phosphoroxchloride and 8-hydroxy quinoline gave the 8-hydroxy-5-acetaminomethyl quinoline (14) (Scheme 7) [14].



(Scheme 7)

The key step in the preparation of the majority of 8-hydroxy-5-aminomethyl quinoline was accomplished readily via acid-catalyzed, nuclear amidoalkylation of an appropriately substituted 8-hydroxy-5-acetaminomethyl quinoline which after subsequent hydrolysis, afforded the target product (15) as indicated in scheme 8 [14].

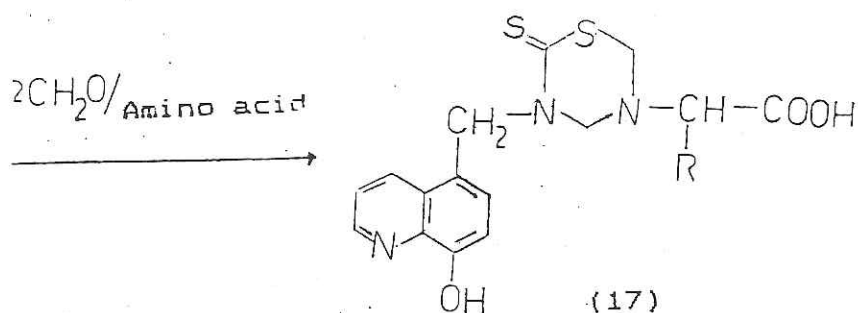
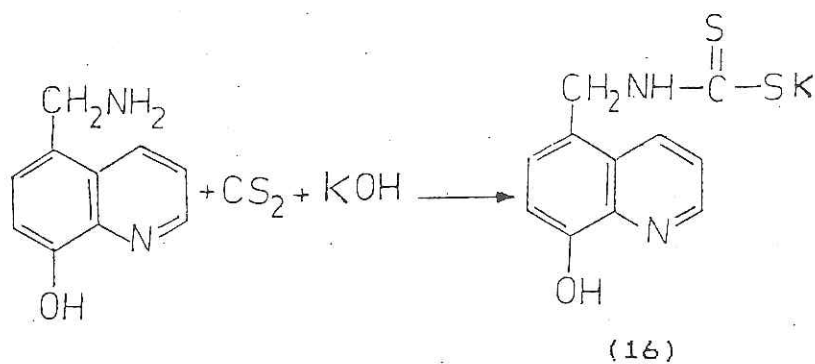


(Scheme 8)

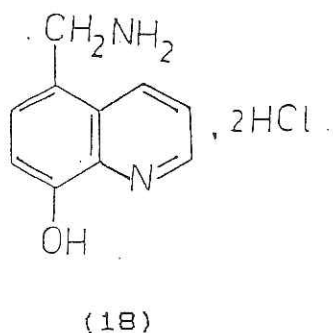
Originally we planned to react 8-hydroxy-5-aminomethyl quinoline with carbon disulfide and potassium hydroxide to give dithiocarbamate (16). Afterwards, dithiocarbamate would react with two moles of formaldehyde and amino acid to give 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives (17) as indicated in scheme 9.

But the preparation of 8-hydroxy-5-aminomethyl quinoline as in free base was not successful. Because the free base could not be isolated by making its aqueous alkaline solution due to its rapid decomposition.

This time, instead of free base hydrochloride salt (18) was used, however, upon the addition of carbon disulfide and potassium hydroxide the expected product (16) could not be obtained probably because of the decomposition of (18) in the basic medium.

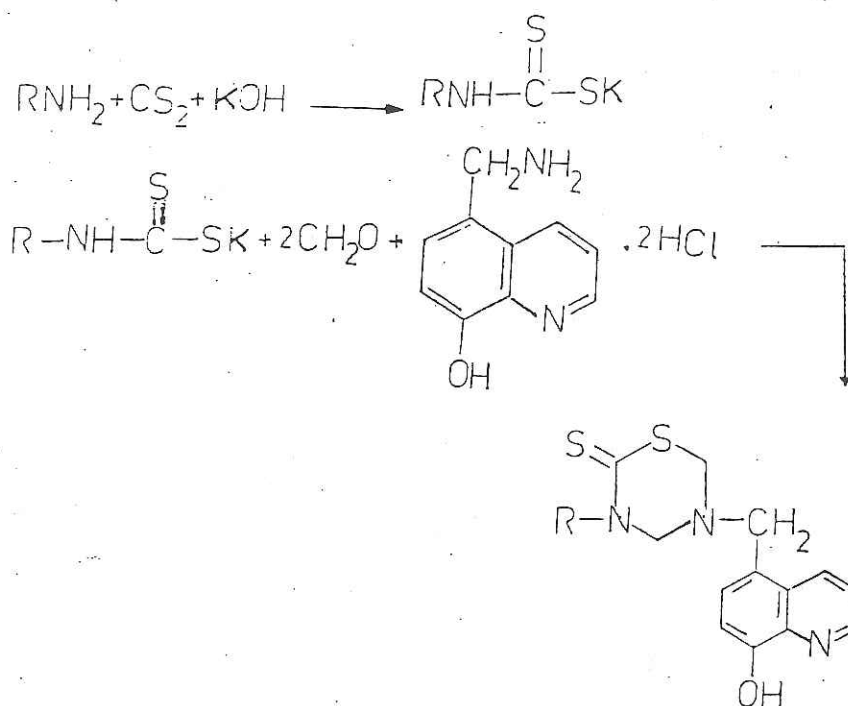


(Scheme 9)



All these effects compelled us to obtain dithiocarbamate from the reaction between a primary amine and carbon disulfide in potassium hydroxide. The treatment of the resulting dithiocarbamate with formaldehyde and 8-

hydroxy-5-aminomethyl quinoline hydrochloride yielded 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione which bears 8-hydroxy-5-methyl quinoline at the 5th position (Scheme 10).



(Scheme 10)

R: methyl, ethyl, isopropyl, isopentyl, n-buthyl, cyclohexyl

The synthesis of 3,5-disubstitued-tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives is shown in scheme 11.

In the first step, equimolar amounts of primary amine was reacted with carbon disulfide in basic medium. The expected nucleophilic attack of primary amine to carbon disulfide gave potassium dithiocarbamate (19).

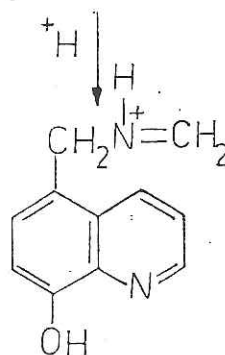
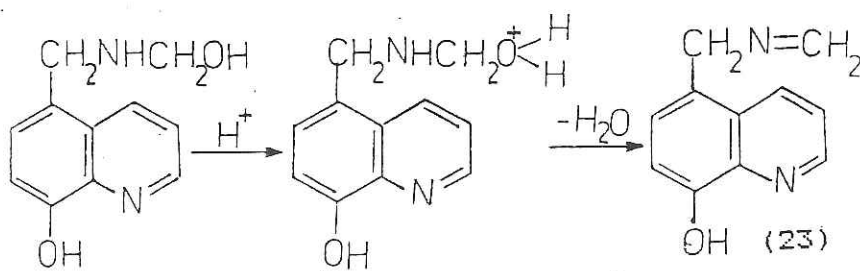
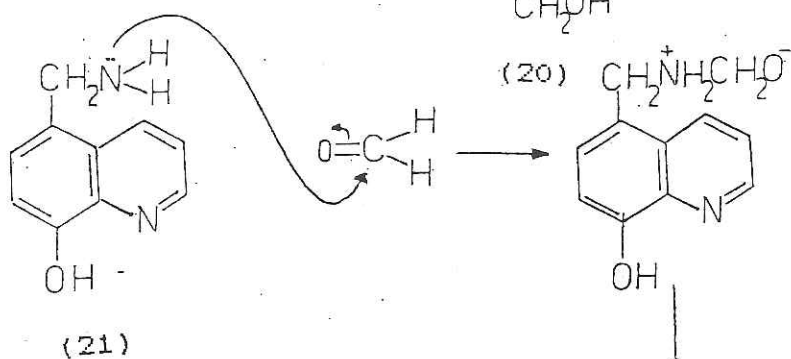
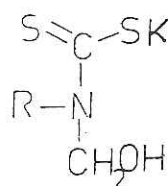
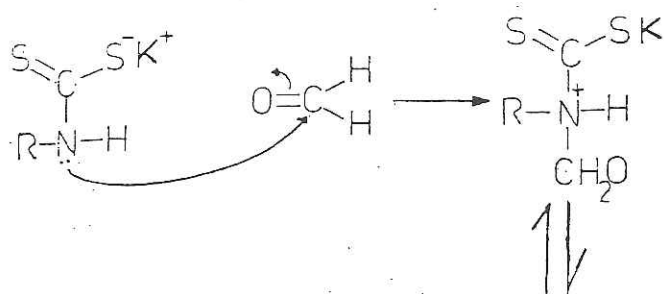
In the second step potassium dithiocarbamate acts as a nucleophile on formaldehyde to give intermediate (20).

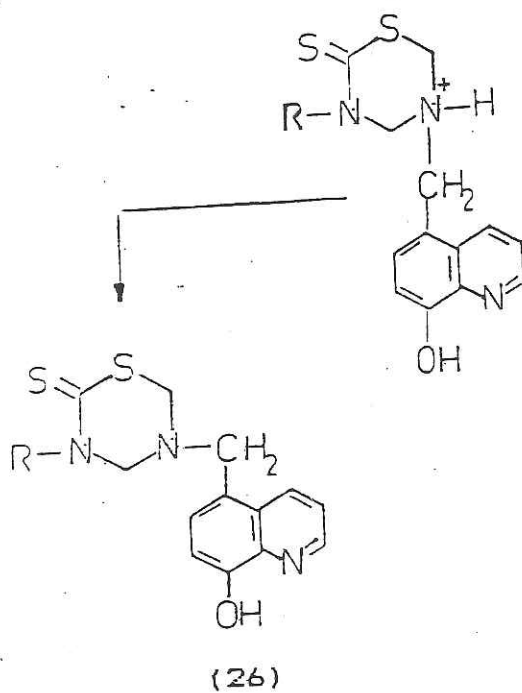
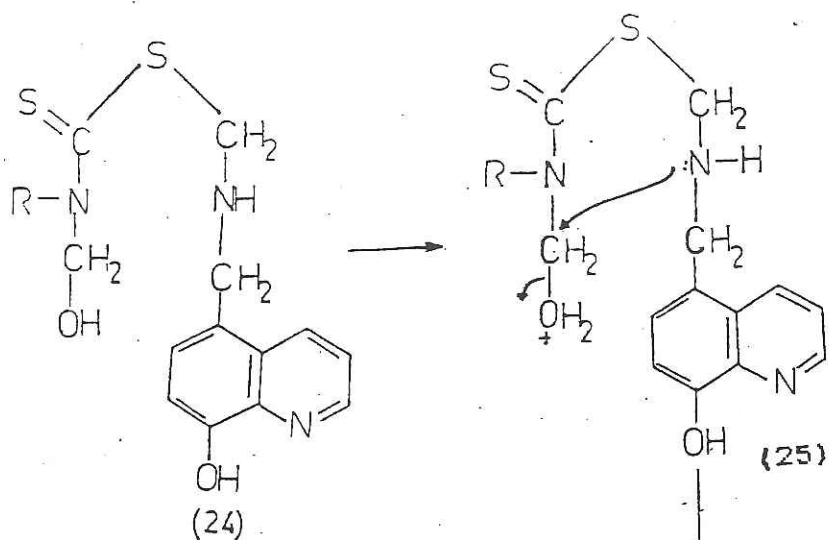
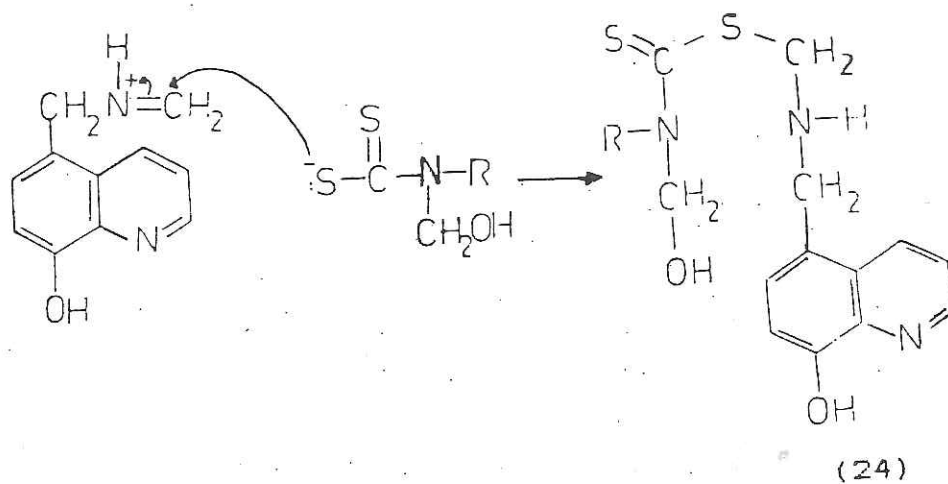
The synthesis of compound (22) was achieved by using 8-hydroxy-5-aminomethyl quinoline (21) and formaldehyde in the third step. Compound (22) was then reacted with compound (20) in acidic medium to give compound (24).

Finally intramolecular attack of amine nitrogen and readily loss of water molecule yields tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives (26) through a cyclization reaction.



(19)





(Scheme 11)

3.2. Decomposition of Tetrahydro-2H-1,3,5-Thiadiazine Derivatives

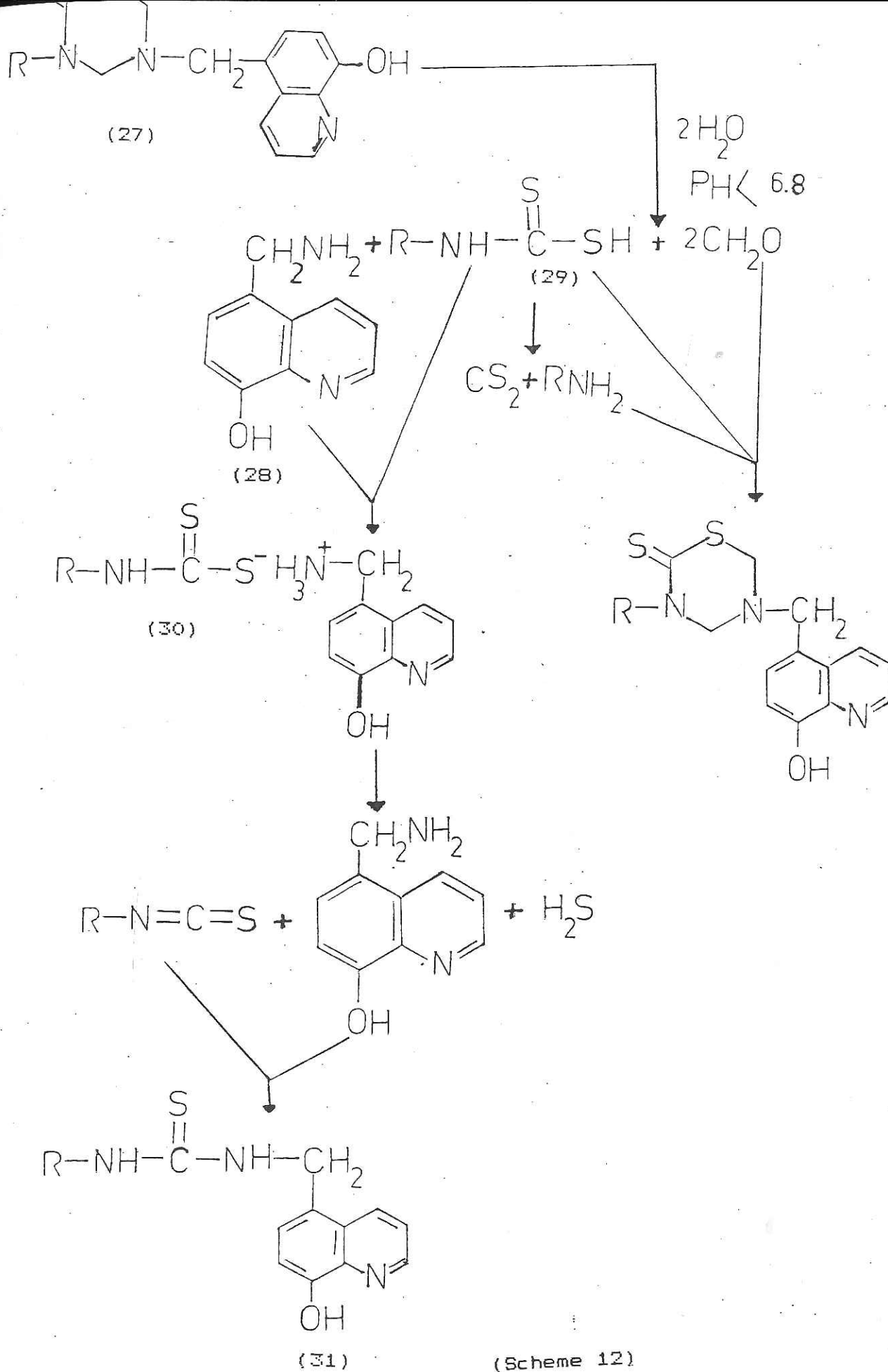
Tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives are decomposed by water or alcohols, particularly at high temperature or in the presence of acids, iodine, nitrous acid or mercuric chloride which causes similar breakdown, dithiocarbamate being formed as well as the three main degradation products, primary amine, formaldehyde, and carbon disulfide [6].

When cyclization reaction of 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione is performed, the reaction can also be reversed as a result of hydrolysis. For this reason some scientists have used suitable solvents such as pyridine, ethanol and organic solvents instead of water. All these works are assumed to increase the yield of products, however, these methods can be agreed as profitable only for derivatives which have same substituents on third and fifth position, but not valid for the derivatives with different substituents on those positions [12,15].

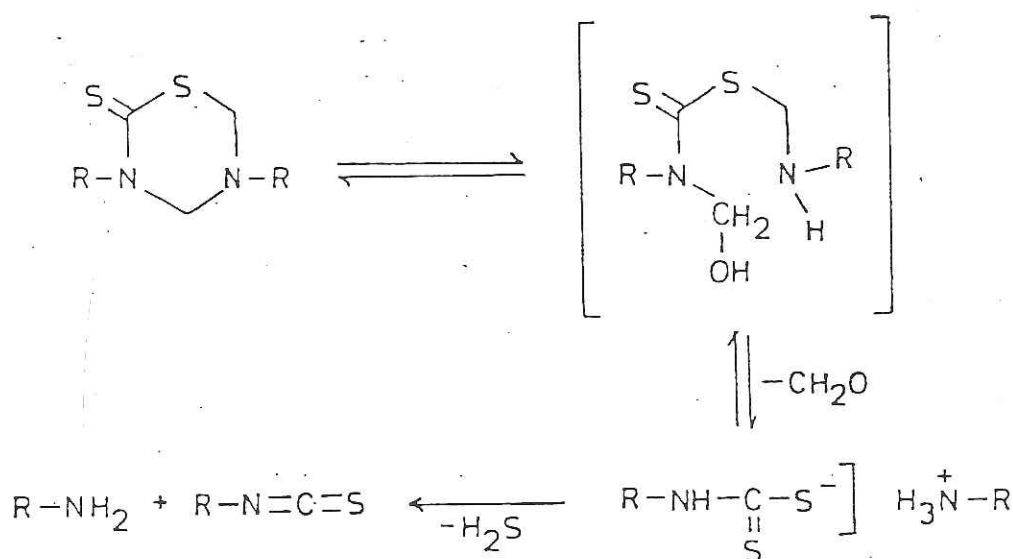
The originally planned compound and the one obtained in the present work, do not contain same substituents at the third and fifth positions. Therefore water has been selected and used as the reaction medium. It is observed that the reaction is more stable at pH values above 6.5. For that reason pH of the solution has been kept above 6.5 and order of percent yields of synthesis reactions are given as 42.0%,

70.4%, 68.0%, 45.0%, 76.1%, 72.0% for 3-methyl-5-(8-hydroxy-5-methyl quinoline) tetrahydro-2H-1,3,5-thiadiazine-2-thione, 3-ethyl-5-(8-hydroxy-5-methyl quinoline) tetrahydro-2H-1,3,5-thiadiazine-2-thione, 3-isopropyl-5-(8-hydroxy-5-methyl quinoline) tetrahydro-2H-1,3,5-thiadiazine-2-thione, 3-n-butyl-5-(8-hydroxy-5-methyl quinoline) tetrahydro-2H-1,3,5-thiadiazine-2-thione, 3-isopentyl-5-(8-hydroxy-5-methyl quinoline) tetrahydro-2H-1,3,5-thiadiazine-2-thione, 3-cyclohexyl-5-(8-hydroxy-5-methyl quinoline) tetrahydro-2H-1,3,5-thiadiazine-2-thione, respectively.

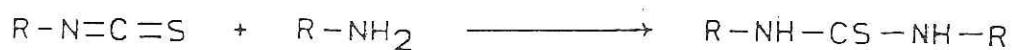
The hydrolysis of 3-alkyl-5-(8-hydroxy-5-methyl quinoline)-tetrahydro-2H-1,3,5-thiadiazine-2-thione (27) derivatives in aqueous acid solution is expected to give formaldehyde, 8-hydroxy-5-aminomethyl quinoline (28) and dithiocarbamate (29). The further decomposition of (29) gives carbon disulfide and primary amine. If dithiocarbamic acid (29) is reacted with 8-hydroxy-5-aminomethyl quinoline (28), 8-hydroxy-5-methyl quinoline ammonium salt of alkyl dithiocarbamic acid (30) can be formed. The decomposition products of (30) are alkyl isothiocyanite, 8-hydroxy-5-aminomethyl quinoline and hydrogen sulfide. When alkyl isothiocyanite is reacted with 8-hydroxy-5-aminomethyl quinoline (28), compound (31) can be obtained (Scheme 12).



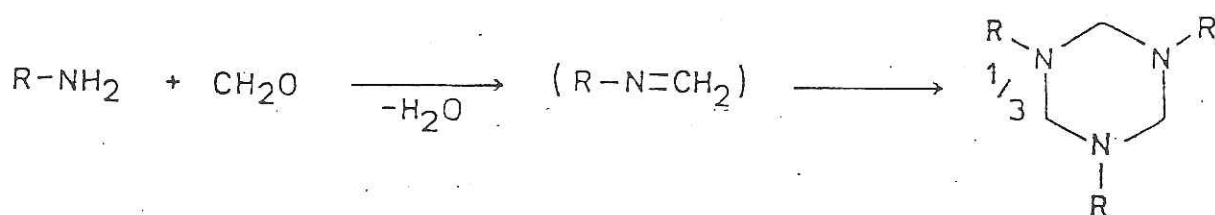
Würbach and his coworkers studied the hydrolysis of these types of compounds. According to them the rate of decomposition is increased with acidity of the medium with respect to the basicity of the medium. They found that the hydrolysis of 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione in acidic medium gives RNH_2 and R-N=C=S by the elimination of formaldehyde and hydrogen sulfide. Furthermore, reactions between the decomposition products and the new compounds formed as a result of these reactions are illustrated in Schemes 13-18.



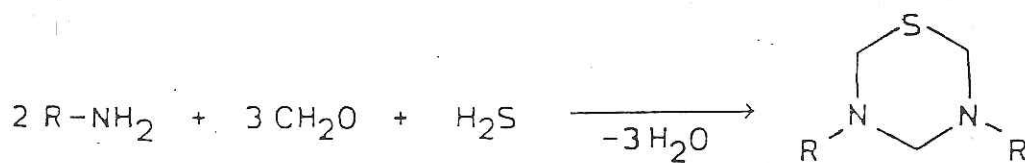
(Scheme 13)



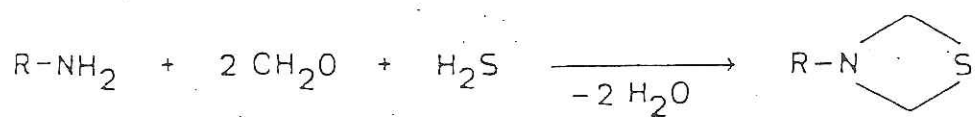
(Scheme 14)



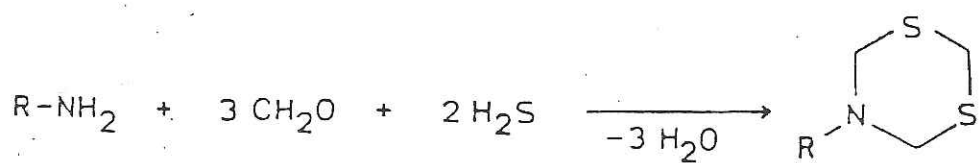
(Scheme 15)



(Scheme 16)



(Scheme 17)



(Scheme 18)

IV. EXPERIMENTAL PART

4.1 Apparatus and Material

The compounds in the present work had been identified by the mentioned instruments below.

Bruker 80 MHz NMR spectrometer and Varian T-60 A 60 MHz NMR spectrometer was used to take NMR spectra. Chloroform- d_1 and DMS was used as solvent and tetramethyl silane as internal standard.

The percentage of C, H, N was detected by using Hewlett-Packard 185 C, H, N analyzer.

The IR spectra were taken on Philips PU 9700 IR spectrophotometer by using potassium bromide disk, sodium chloride cells and chloroform as solvent.

Shimadzu UV 160 UV spectrophotometer was used to take UV spectra of compounds by using chloroform as solvent.

Melting points of compounds were determined on Reichert hot stage melting point apparatus.

4.2. General Method for the Preparation of Derivatives

3.45×10^{-3} mole of primary amine was dissolved in water and stirred with 3.45×10^{-3} mole of 20% potassium hydroxide and 3.45×10^{-3} mole of carbon disulfide was added to the mixture. Stirring continued approximately 3 hours at room

temperature. When clear orange solution was obtained 6.90×10^{-3} mole of 37% formaldehyde was added on the same mixture. After stirring for 15 minutes, aqueous 8-hydroxy-5-aminomethyl quinoline was added dropwise to the reaction mixture and was stirred for 1 hour.

4.3. Preparations

4.3.1. Synthesis of N-N'-Methylene bis acetamide

The synthesis of N-N'-Methylene bis acetamide was accomplished by modifying a known method [13]. It was prepared by condensation of >1 mole of paraformaldehyde and 2 moles of acetamide. Thus 9.0 g acetamid and 3.2 g paraformaldehyde were heated 20 hours at 140-50°C and 100 mmHg. The product was recrystallized from ethanol. (8.9 g, 89%) m.p.:195°C (Lit.195°C);

$^1\text{H-NMR}$ (DMS-int TMS):

δ (ppm) 3.2 (s, 6H, CH_3)

5.8 (t, 2H, CH_2)

9.0 (s, 2H, NH)

IR (KBr) ν_{max} : 3230, 3080, 1640 cm^{-1}

4.3.2. Synthesis of 8-Hydroxy-5-Acetaminomethyl Quinoline

The synthesis of 8-hydroxy-5-acetaminomethyl quinoline was accomplished by modifying a known method [14] as follows;

3.5 g 8-hydroxy quinoline was added to 4 g bis acetamid and 2 g POCl_3 . The mixture was stirred with a mechanical stirrer at 95°C for 2 hours. Then the mixture was neutralized with sodium carbonate solution and extracted with chloroform. Chloroform phase was dried with MgSO_4 and solvent was evaporated. The product was recrystallized from ethanol (2.08 g, 40%). M.p.: 184°C (Lit. 184°C).

$^1\text{H-NMR}$ (DMS-int TMS):

$\delta(\text{ppm})$ 2.0 (s, 3H, CH_3)
 4.0 (d, 1H, NH)
 4.9 (d, 2H, CH_2)
 7.2-8.2(m, 5H, quinoline)

IR (KBr): ν_{max} : 3300, 1640 cm^{-1}

4.3.3. Synthesis of 8-hydroxy-5-Aminomethyl Quinoline hydrochloride

8-Hydroxy-5-aminomethyl quinoline hydrochloride was obtained from the hydrolysis of 8-hydroxy-5-acetaminomethyl quinoline in concentrated HCl by refluxing periodically. m.p.: $> 360^\circ\text{C}$.

$^1\text{H-NMR}$ (CDCl_3 -int TMS):

$\delta(\text{ppm})$ 4.75 (s, 2H, CH_2)
 H_a 9.0-9.3 (d, 1H, aromatic CH)
 H_b 7.3-7.4 (d, 1H, aromatic CH)
 H_c 9.4-9.7 (d, 1H, aromatic CH)
 H_e 8.1-8.4 (d, 1H, aromatic CH)
 H_f 7.8-8.1 (t, 1H, aromatic CH)

IR (KBr): ν_{max} : 3480-3420 (broad), $3030-2830\text{ cm}^{-1}$ (broad)

4.3.4. 3-Methyl-5-(8-hydroxy-5-methyl quinoline) Tetrahydro-
2H-1,3,5-Thiadiazine-2-Thione

The compound was obtained as mentioned in general method and crystallized from chloroform: petroleum ether. Yield: 42%, m.p.: 77°C.

$^1\text{H-NMR}$ (CDCl_3 -int TMS)

δ (ppm): 3.38 (s, 3H, CH_3)
4.24 (s, 2H, CH_2 -quinoline)
4.30 (s, 2H, thiadiazine 6- CH_2)
4.38 (s, 2H, thiadiazine 4- CH_2)
7-9 (m, 5H, quinoline)

IR (KBr) ν_{max} : 3400, 2875, 1580, 1500 cm^{-1}

UV (CHCl_3) λ_{max} : 245.8 nm ($\log \epsilon$: 3.698),
291.0 nm ($\log \epsilon$: 3.269)

4.3.5. 3-Ethyl-5-(8-hydroxy-5-methyl quinoline) Tetrahydro-
2H-1,3,5-Thiadiazine-2-Thione

The compound was prepared according to the general method and crystallized from chloroform: petroleum ether. Yield: 70.4%, m.p.: 98°C.

$^1\text{H-NMR}$ (CDCl_3 -int TMS) :

δ (ppm): 1.27 (t, 3H, CH_3 - CH_2)
4.11 (m, 2H, CH_3 - CH_2)
4.27 (d, 4H, thiadiazine 4 and 6- CH_2)
4.32 (s, 2H, CH_2 -quinoline)
7-9 (m, 5H, quinoline)

IR (KBr) ν_{\max} : 3300, 2880, 1580, 1500 cm^{-1}

UV (CHCl_3) λ_{\max} : 248.1 nm ($\log \epsilon = 3.695$),
290.2 nm ($\log \epsilon = 2.982$)

4.3.6. 3-Isopropyl-5-(8-hydroxy-5-methyl quinoline)tetrahydro-
2H-1,3,5-thiadiazine-2-thione

The compound was obtained according to the method mentioned above and crystallized from ether: petroleum ether. Yield: 68.25%, m.p.: 78°C.

$^1\text{H-NMR}$ (CDCl_3 -int TMS) :

δ (ppm): 1.20 (d, 6H, 2CH_3)
4.20 (d, 4H, thiadiazine 4 and 6 CH_2)
4.40 (s, 2H, CH_2 -quinoline)
4.5-5 (m, 1H, $\text{CH}(\text{CH}_3)_2$)
7-9 (m, 5H, quinoline)

IR (KBr) ν_{\max} : 3300, 2880, 1580, 1500 cm^{-1}

UV (CHCl_3) λ_{\max} : 246.6 nm ($\log \epsilon = 3.550$),
291.0 nm ($\log \epsilon = 2.846$)

4.3.7. 3-n-butyl-5-(8-hydroxy-5-methyl quinoline)tetrahydro-
2H-1,3,5-thiadiazine-2-thione

The compound was obtained as described and washed with ether. Yield: 45.00%, m.p.: 93°C.

$^1\text{H-NMR}$ (CDCl_3 -int TMS) :

δ (ppm): 0.90 (d, 3H, CH_3)
1.50 (m, 2H, CH_3 - CH_2 - CH_2 - CH_2 -)

3.60 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-N}$)

4.10 (t, 2H, $\text{CH}_2\text{-N}$)

4.40 (s, 4H, thiadiazine-4 and $\text{CH}_2\text{-}$
quinoline)

5.00 (s, 2H, thiadiazine 4- CH_2)

7-9 (m, 5H, quinoline)

IR (KBr) ν_{max} : 3300, 2880, 1580, 1500 cm^{-1}

UV (CHCl_3) λ_{max} : 246.9 nm ($\log \epsilon = 3.821$),
290.3 nm ($\log \epsilon = 3.433$)

4.3.8. 3-Isopentyl-5-(8-hydroxy-5-methyl quinoline)tetrahydro-
2H-1,3,5-thiadiazine-2-thione

The compound was obtained as before and crystallized
from chloroform; petroleum ether. Yield: 76.10%, m.p.: 78°C.

$^1\text{H-NMR}$ (CDCl_3 -int TMS) :

δ (ppm): 0.90 (d, 6H, 2CH_3)

1.50 (m, 2H, $-\text{CH}-\text{CH}_2\text{-CH}_2\text{-}$)

3.00 (m, 1H, $\text{CH}(\text{CH}_3)_2$)

3.90 (m, 2H, $\text{CH}_2\text{-N}$)

4.20 (s, 2H, $\text{CH}_2\text{-quinoline}$)

4.40 (s, 4H, thiadiazine 4-and 6 CH_2)

7-9 (m, 5H, quinoline)

IR (KBr) ν_{max} : 3300, 2880, 1580, 1500 cm^{-1}

UV (CHCl_3) λ_{max} : 247.1 nm ($\log \epsilon = 3.924$),
291.4 nm ($\log \epsilon = 3.386$)

4.3.9. 3-Cyclohexyl-5-(8-hydroxy-5-methyl quinoline)tetrahydro-
2H-1,3,5-thiadiazine-2-thione

The compound was obtained according to the general preparation method and crystallization from chloroform: petroleum ether. Yield: 72%, m.p.: 75°C.

$^1\text{H-NMR}$ (CDCl_3 -int TMS) :

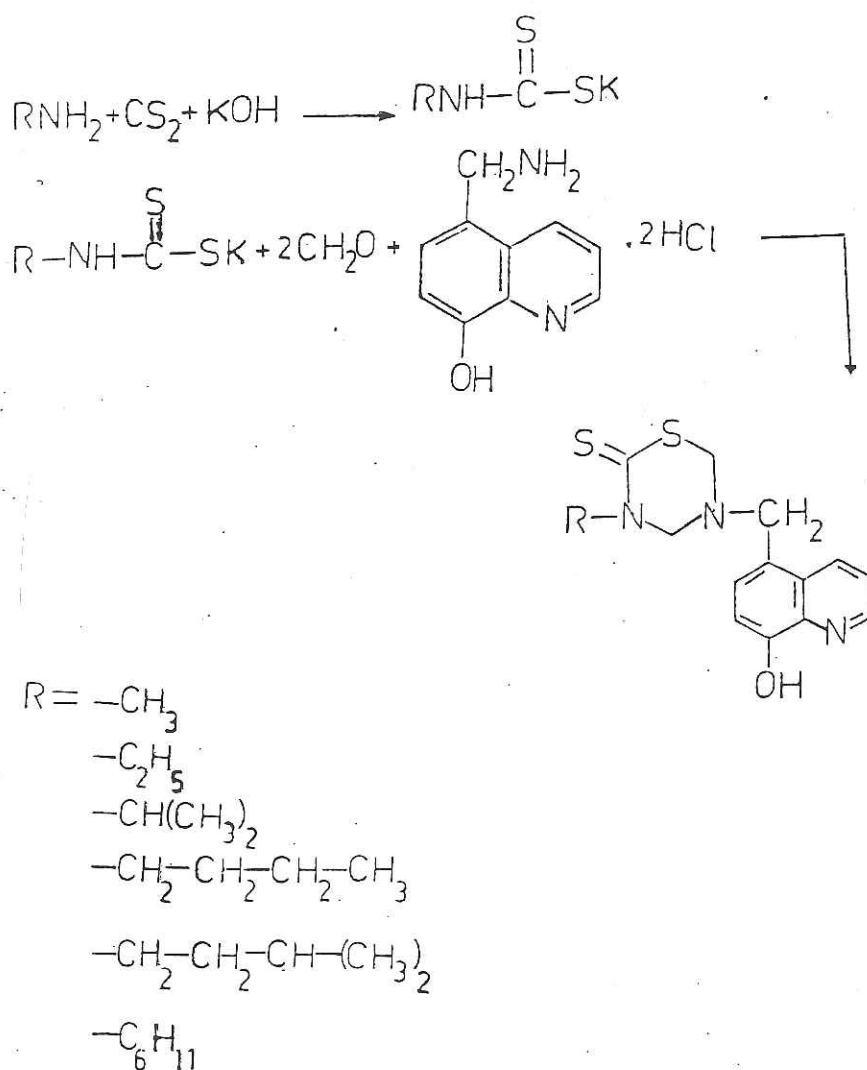
δ (ppm): 1-2 (m, 10H, cyclohexyl)
4.10 (s, 2H, CH_2 -quinoline)
4.40 (m, 1H, CH-cyclohexyl)
4.70 (s, 2H, thiadiazine 6- CH_2)
5.00 (s, 2H, thiadiazine-4- CH_2)
7-9 (m, 5H, quinoline)

IR (KBr) ν_{max} : 3300, 2880, 1580, 1480 cm^{-1}

UV (CHCl_3) λ_{max} : 246.9 nm ($\log \epsilon = 3.887$),
281.4 nm ($\log \epsilon = 3.266$)

V. RESULTS AND DISCUSSION

Alkali salts of dithiocarbamic acid were obtained by the reaction between six different primary amines, CS_2 and KOH . Then formaldehyde and 8-hydroxy-5-aminomethyl quinoline was added to the salts. After that, six new 3-amine-5-(8-hydroxy-5-methyl quinoline)-tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives were obtained (Scheme 19)



(Scheme 19)

As already been mentioned, originally 3-(8-hydroxy-5-methyl quinoline)-5-[α -(substitute)-carboxy methyl]-tetrahydro-2H-1,3,5-thiadiazine-2-thione compounds were planned to be synthesized by the reaction of 8-hydroxy-5-amino methyl quinoline dithiocarbamate potassium salts with formaldehyde and different amino acids. Whereas, 8-hydroxy-5-aminomethyl quinoline dithiocarbamate potassium salts were obtained by the addition of carbon disulfide and potassium hydroxide into 8-hydroxy-5-amino methyl quinoline. Unfortunately, this proposed synthesis failed due to the rapid decomposition of 8-hydroxy-5-amino methyl quinoline in the basic medium. For this reason a minor modification was made on the target compound, and planned to synthesize compound (6). There are two main differences between these two compounds (compound 6,17). The 8-hydroxy-5-amino methyl quinoline group, expected to appear at the third position in the desired product, was found at the fifth position in the resultant product and instead, an alkyl group was attached to the amine at the third position. The α -(substitute) carboxymethyl group in the original structure was not considered at all.

The importance of substituents at third and fifth positions on 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives was pointed out regarding to their activities. Therefore primary amines were used at the third position and because of antifungal effect, 8-hydroxy-5-amino methyl quinoline was used at the fifth position.

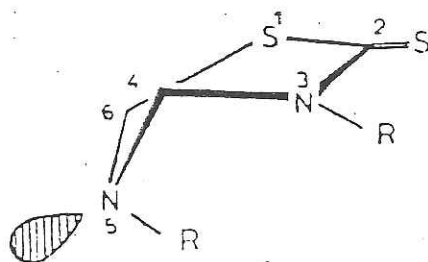
The spectrum of the 3,5-disubstituted-tetrahydro-2H-1,3,5-thiadiazine-2-thione derivatives give two electrostatic absorption peaks at 250 nm and 290 nm, Carbon sulfide double bond and unpaired electrons on nitrogen atom or unpaired electrons on sulfur atom have shown $\pi-\pi^*$ and $n-\pi^*$ transitions [17].

In the spectrophotometric studies maximum absorption peaks may be changed depending on the substituents attached to the third and fifth positions. Consequently, there were slight changes in experimental and theoretical values. UV absorbance was found between 242 and 255 nm instead of 250 nm, and between 283 and 292 nm instead of 290 nm.

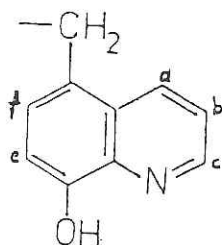
The observation of NMR spectra of these compounds have shown that hydrogen atoms possess the desired chemical shift and integral values in the structure. These data are in good agreement with those reported in literature for tetrahydro-2H-1,3,5-thiadiazine-2-thione ring.

The protons at the sixth position of tetrahydro-2H-1,3,5-thiadiazine-2-thione ring appear as a singlet at approximately 4.2-4.7 ppm, however, it has been reported that the protons at the fourth position may as well appear at the same ppm range. For some derivatives of that ring CH_2 protons at the 4th position have been observed a singlet at 4.4-5.1 ppm whereas for others they have appeared as doublets in favor of AB system due to paramagnetic and diamagnetic shift of 0.2 ppm. Semichair conformation,

tautomerism of tetrahydro-2H-1,3,5-thiadiazine-2-thione ring and the presence of magnetic anisotropy are all good evidence for the observations explained above.



The peak of the CH_2 proton which is between the $\text{N}^{(5)}$ and the quinoline ring give a singlet peak at 4.3-4.6 ppm, 8-hydroxy quinoline give multiplet peaks at 7-9 ppm. These multiplet peaks come from the different position of the compound such as;



Peak (ppm)	(CH_2) group
d 8.4-8.5	a
d.d 7.2-7.47	b
d 8.7-8.8	c
d 7.47-7.5	e
d 7.44-7.47	f

In IR spectra OH group is observed in between 3400-3200 cm^{-1} , CH in between 3000-2800 cm^{-1} , C=C in between 1580-1600 cm^{-1} , C=S in between 1520-1480 cm^{-1} . These results are consistent with the data found in the literature for structurally similar compounds.

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APPENDIX

THE NMR AND IR SPECTRUM OF SUBSTANCES

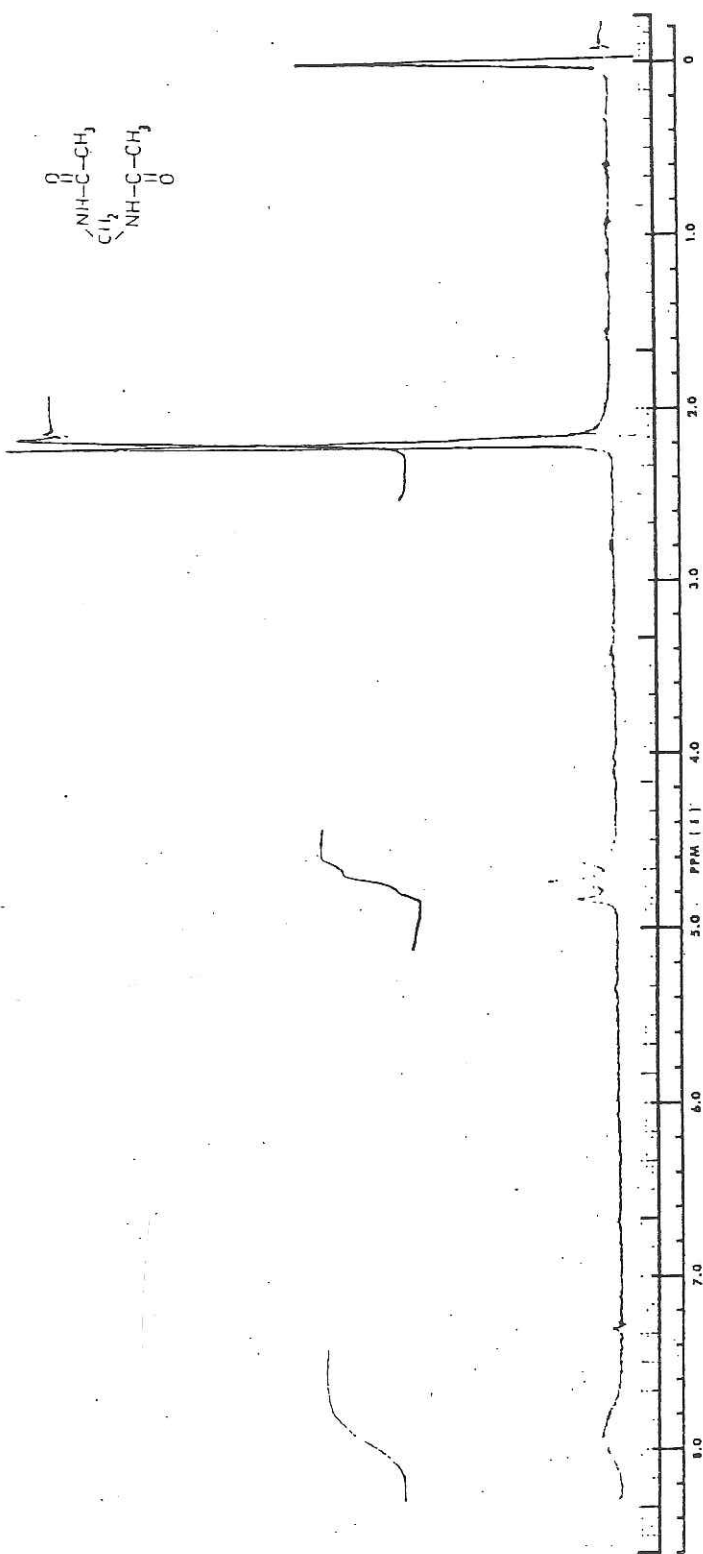


Figure 1. The NMR Spectrum of N-N'-Methylenebis Acetamide

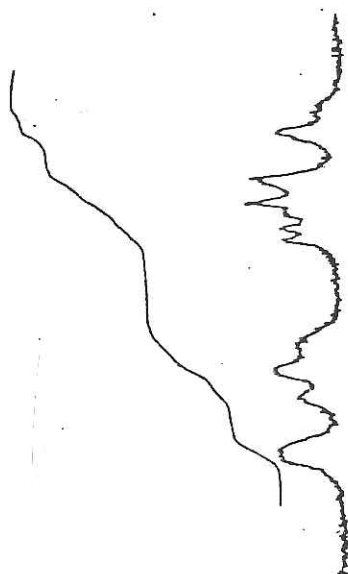


Figure 2. The NMR Spectrum of 8-Hydroxy-5-Acet-Aminomethyl Quinoline

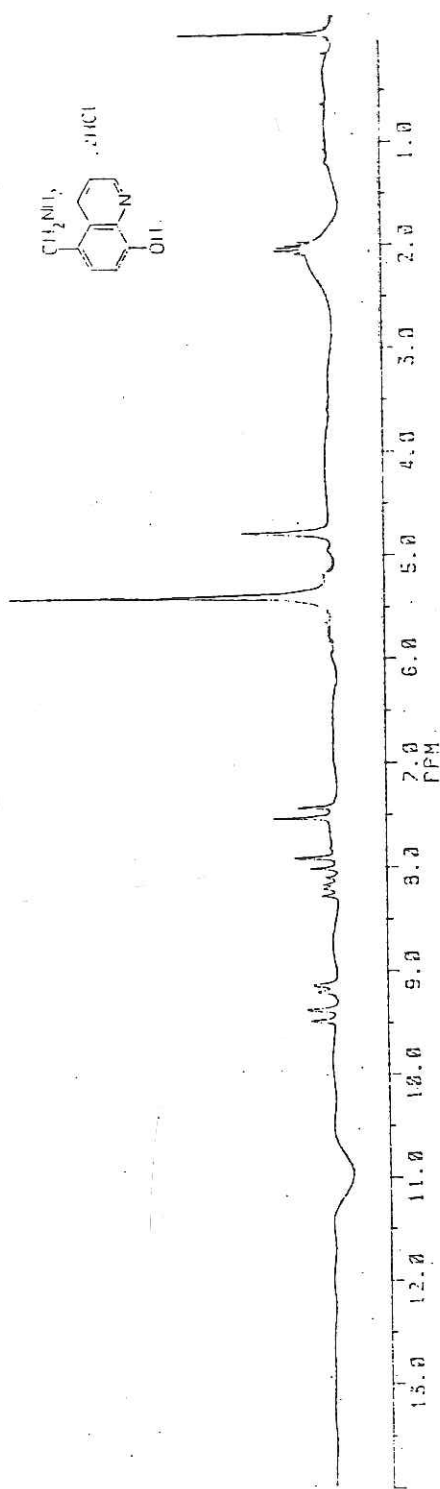


Figure 3. The NMR Spectrum of 8-Hydroxy-5-Aminomethyl Quinoline Hydrochloride

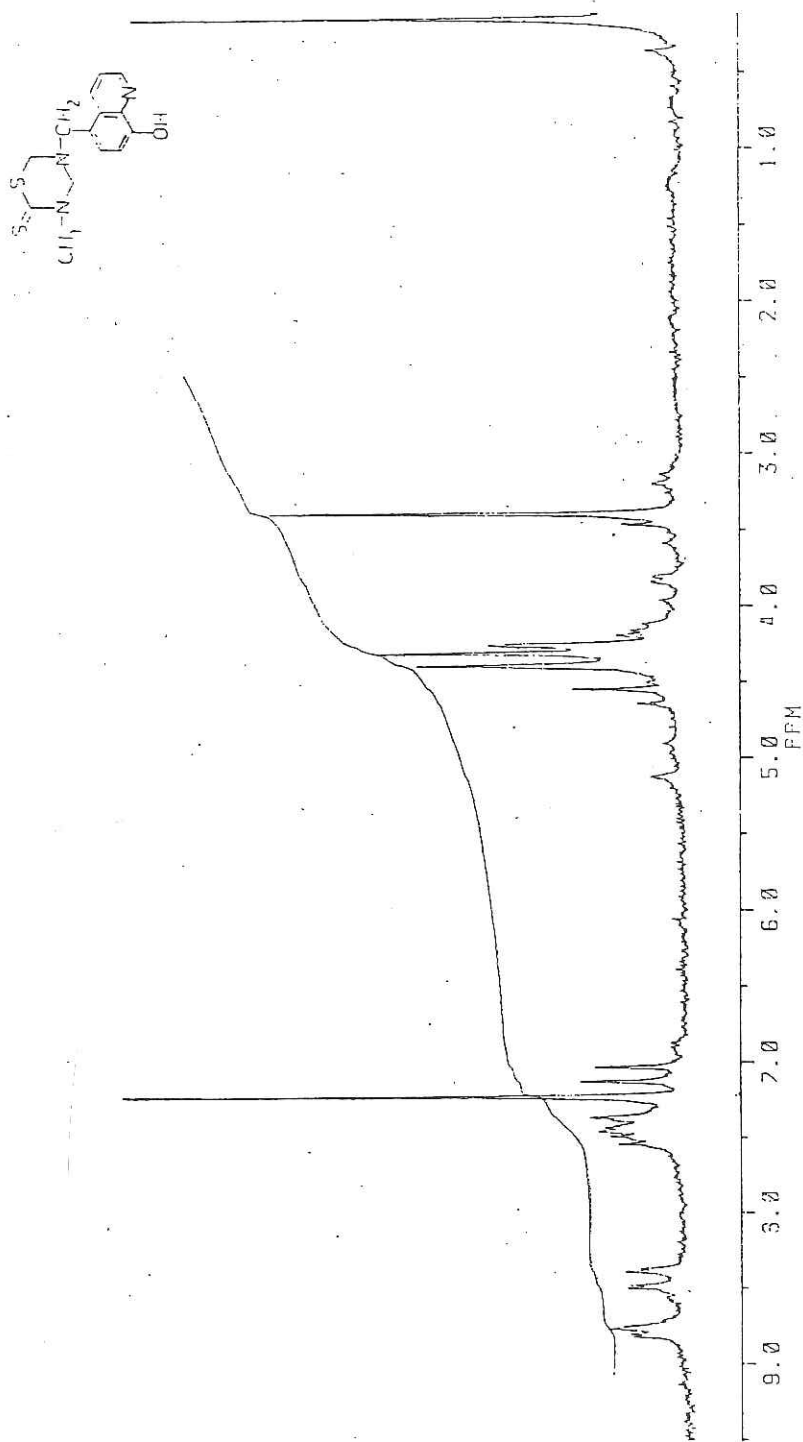


Figure 4. The NMR Spectrum of 3-Methyl-5-(8-Hydroxy-5-Methyl Quinoline)

Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

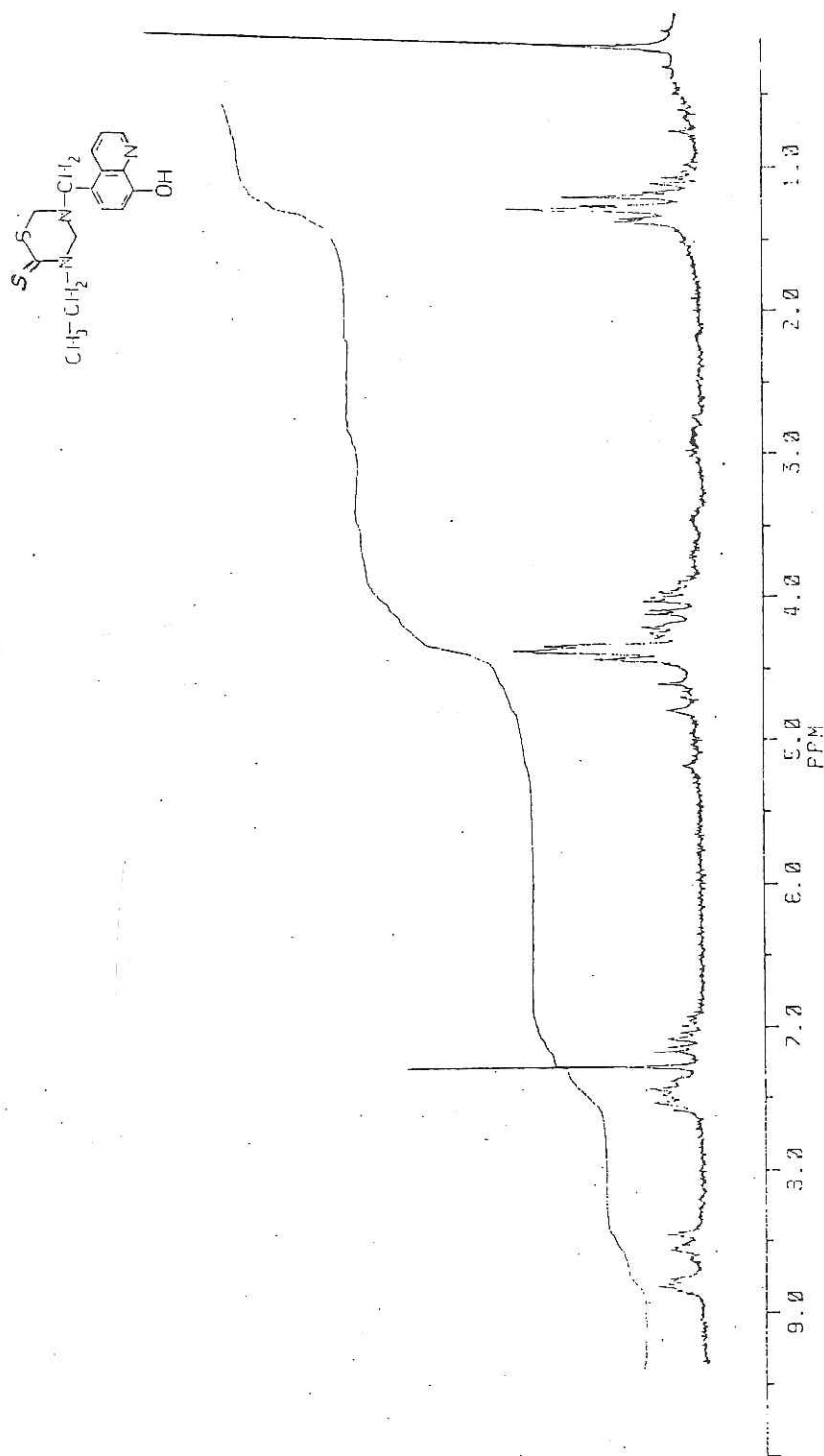


Figure 5. The NMR Spectrum of 3-Ethyl-5-(8-Hydroxy-5-Methyl Quinoline) Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

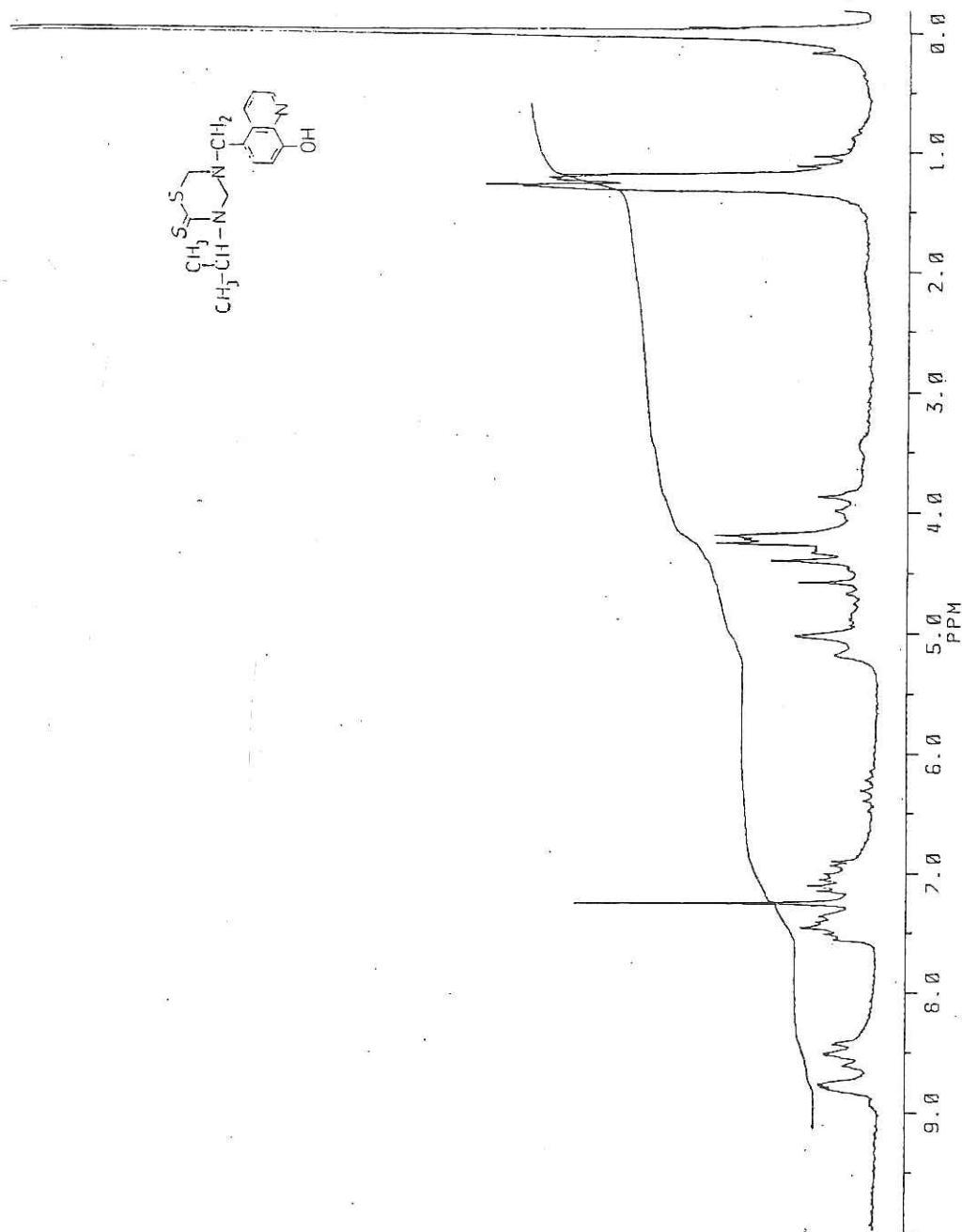


Figure 6. The NMR Spectrum of 3-Isopropyl-5-(8-Hydroxy-5-Methyl Quinoline)

Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

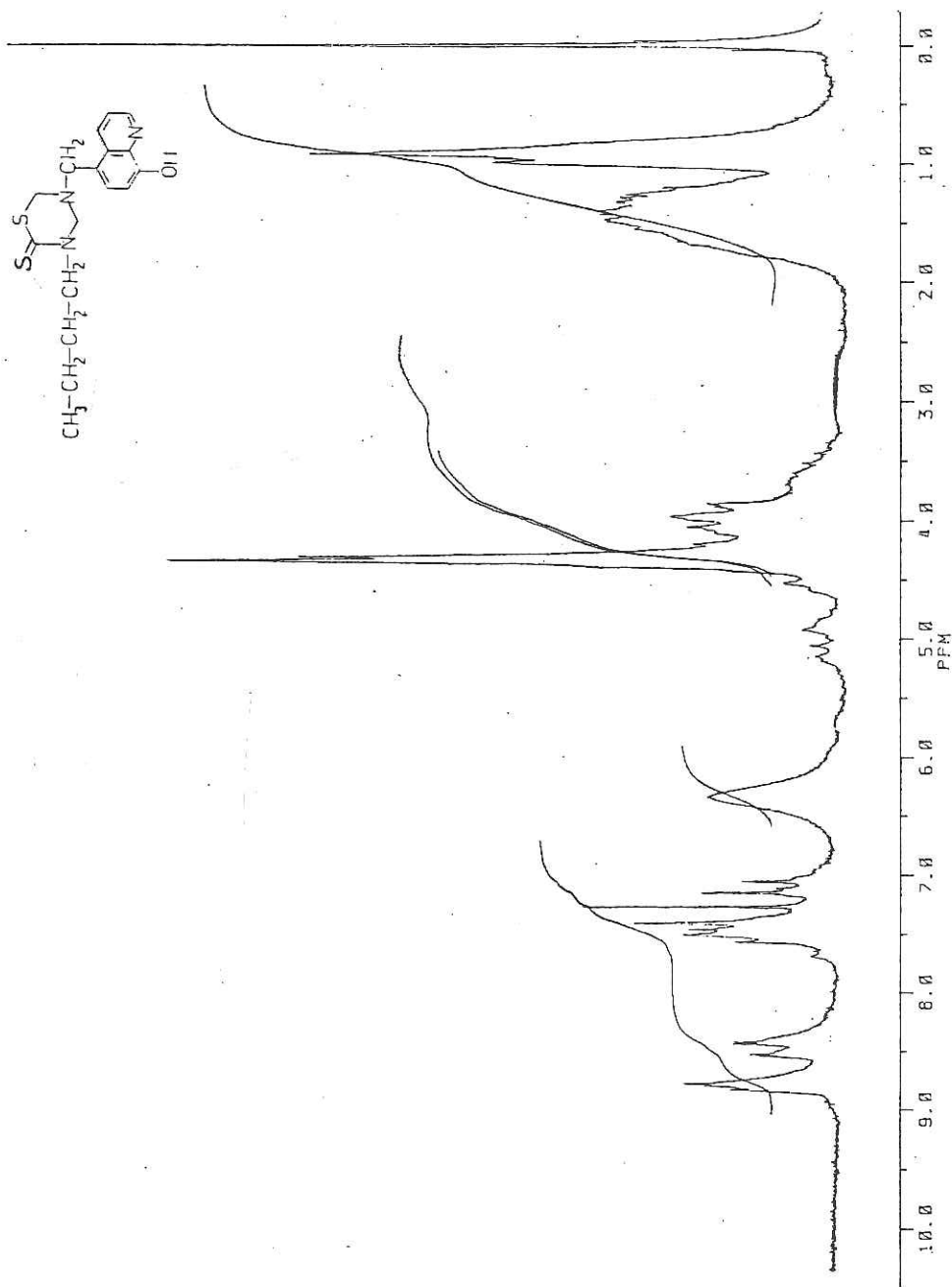


Figure 7. The NMR Spectrum of 3-n-Butyl-5-(8-Hydroxy-5-Methyl Quinoline) Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

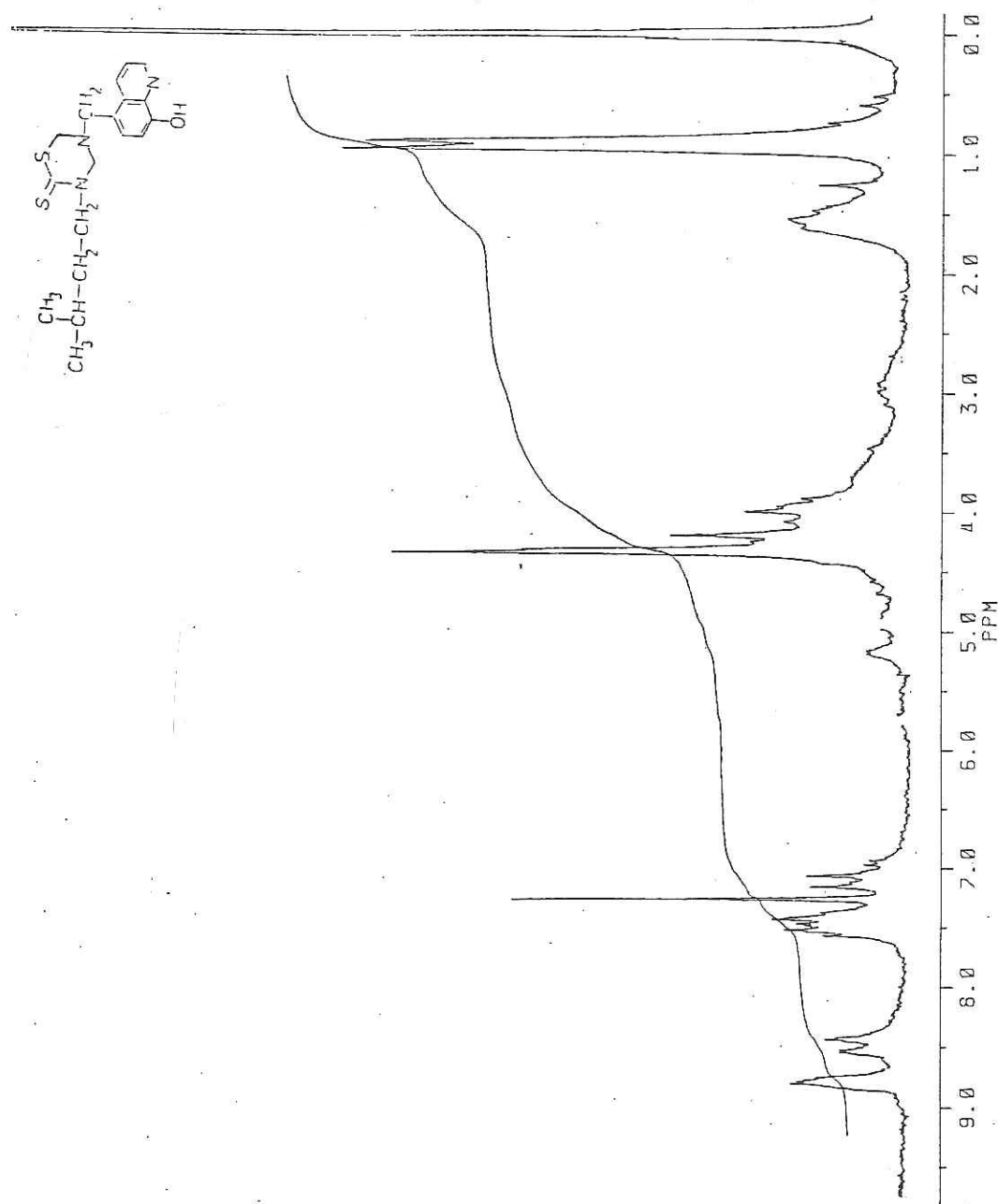


Figure 8. The NMR Spectrum of 3-isopentyl-5-(8-Hydroxy-5-Methyl Quinoline)

Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

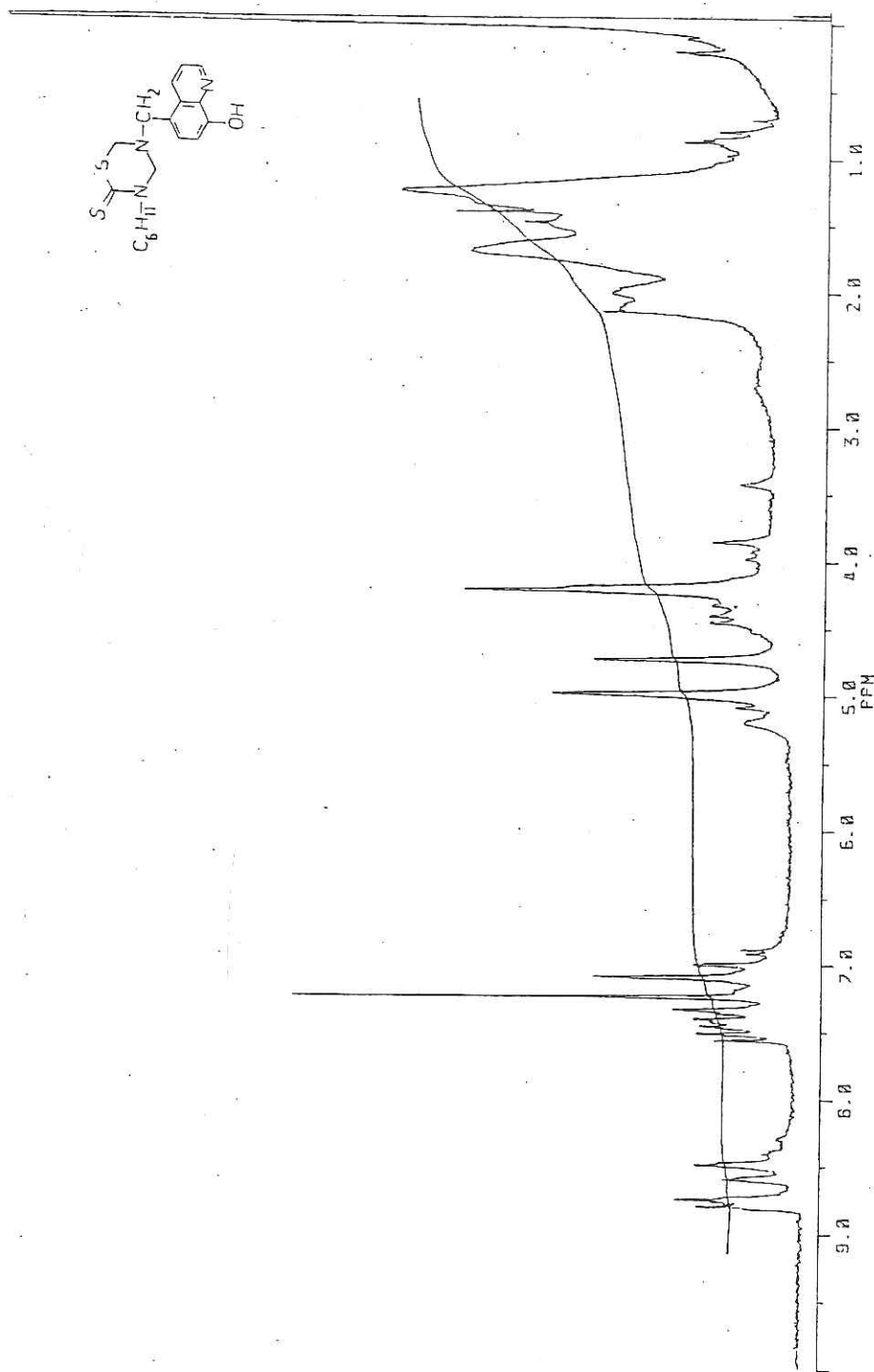


Figure 9. The NMR Spectrum of 3-cyclohexyl-5-(8-Hydroxy-5-Methyl Quinoline)
Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

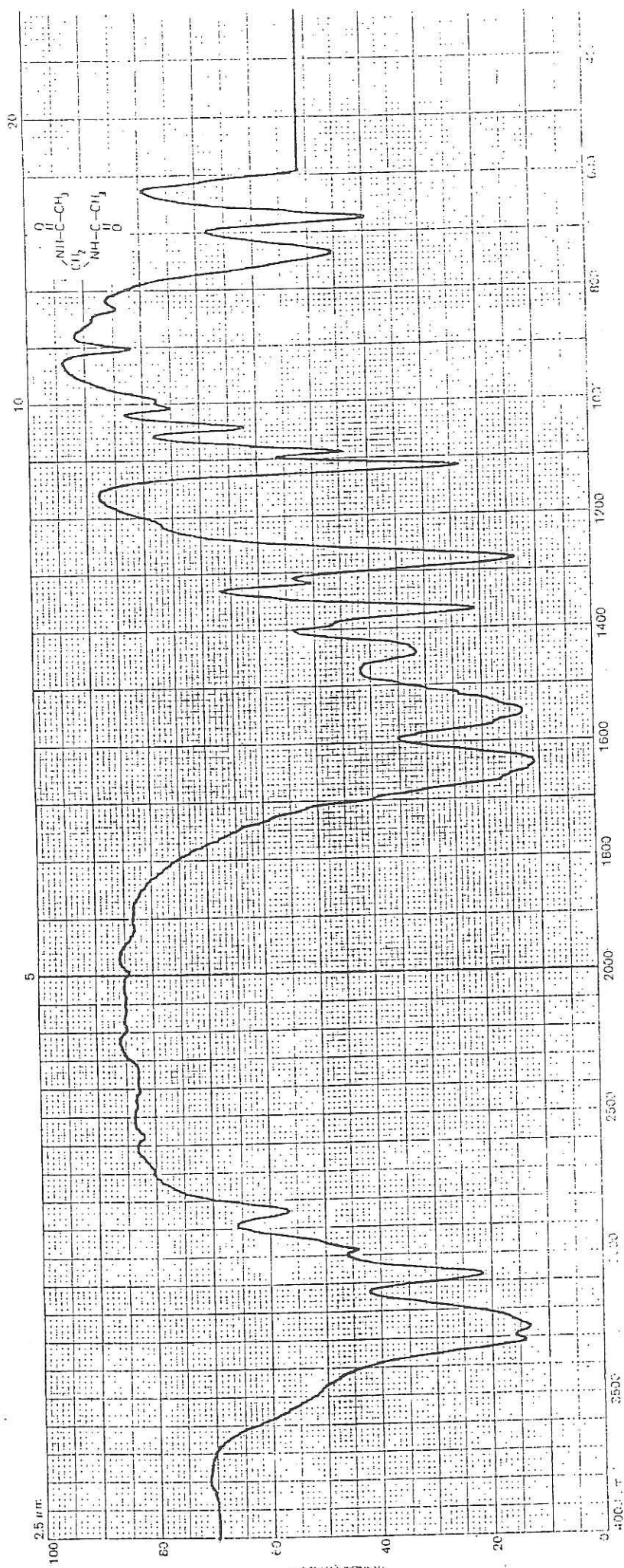


Figure 10. The IR Spectrum of N-N'-Methylenebis Acetamide

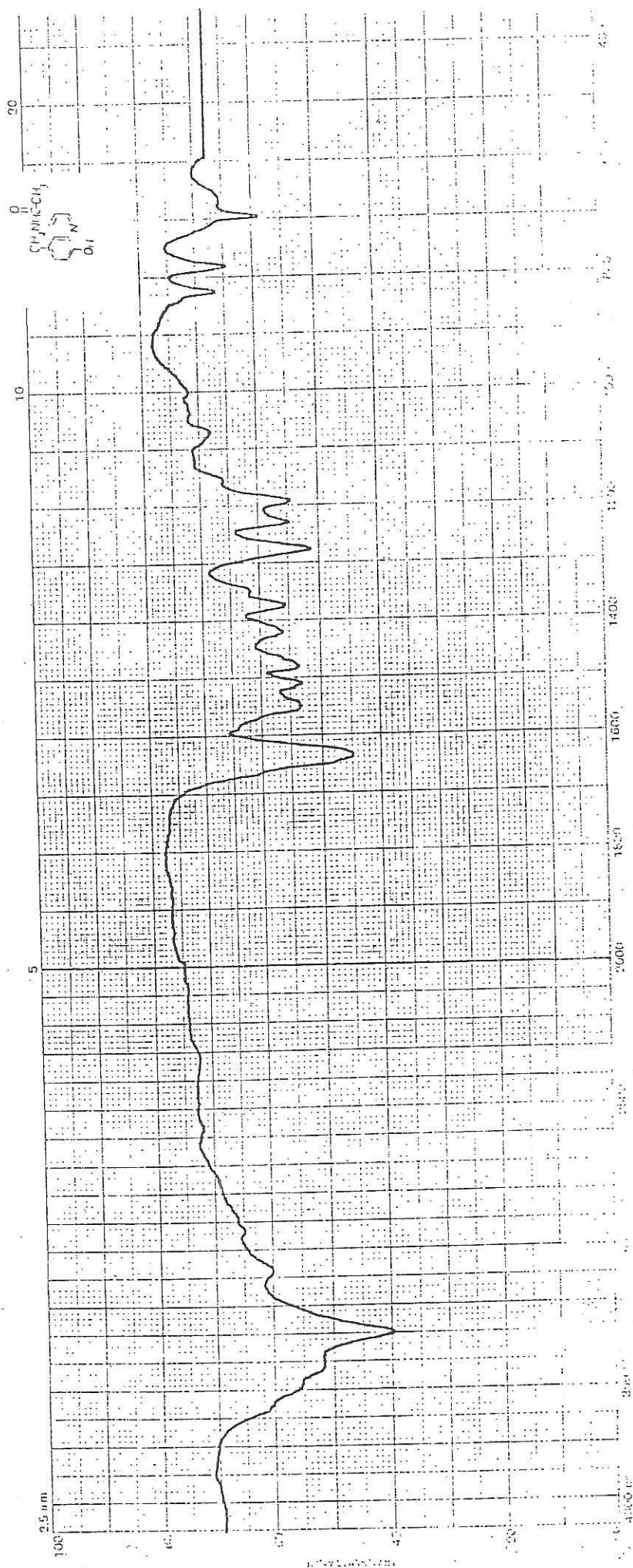


Figure 11. The IR Spectrum of 8-Hydroxy-5-Acet-Aminomethyl Quinoline

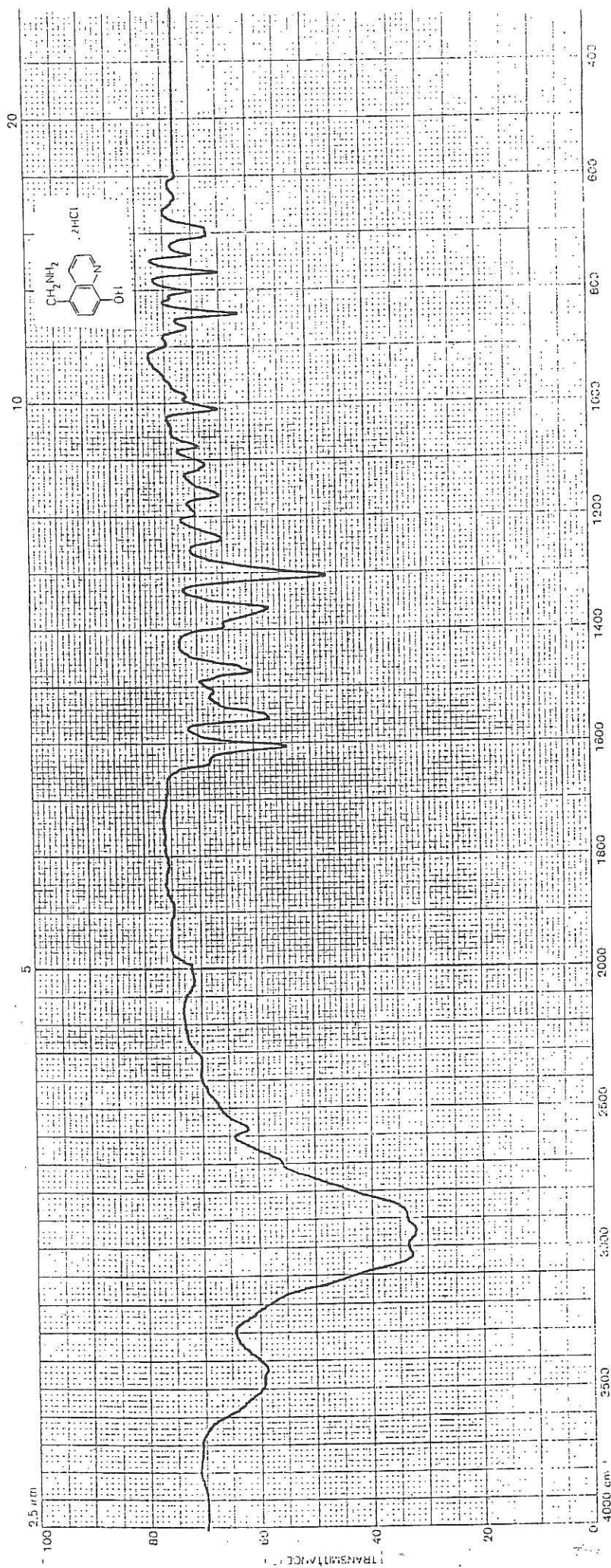


Figure 12. The IR Spectrum of 8-Hydroxy-5-Aminomethyl Quinoline Hydrochloride

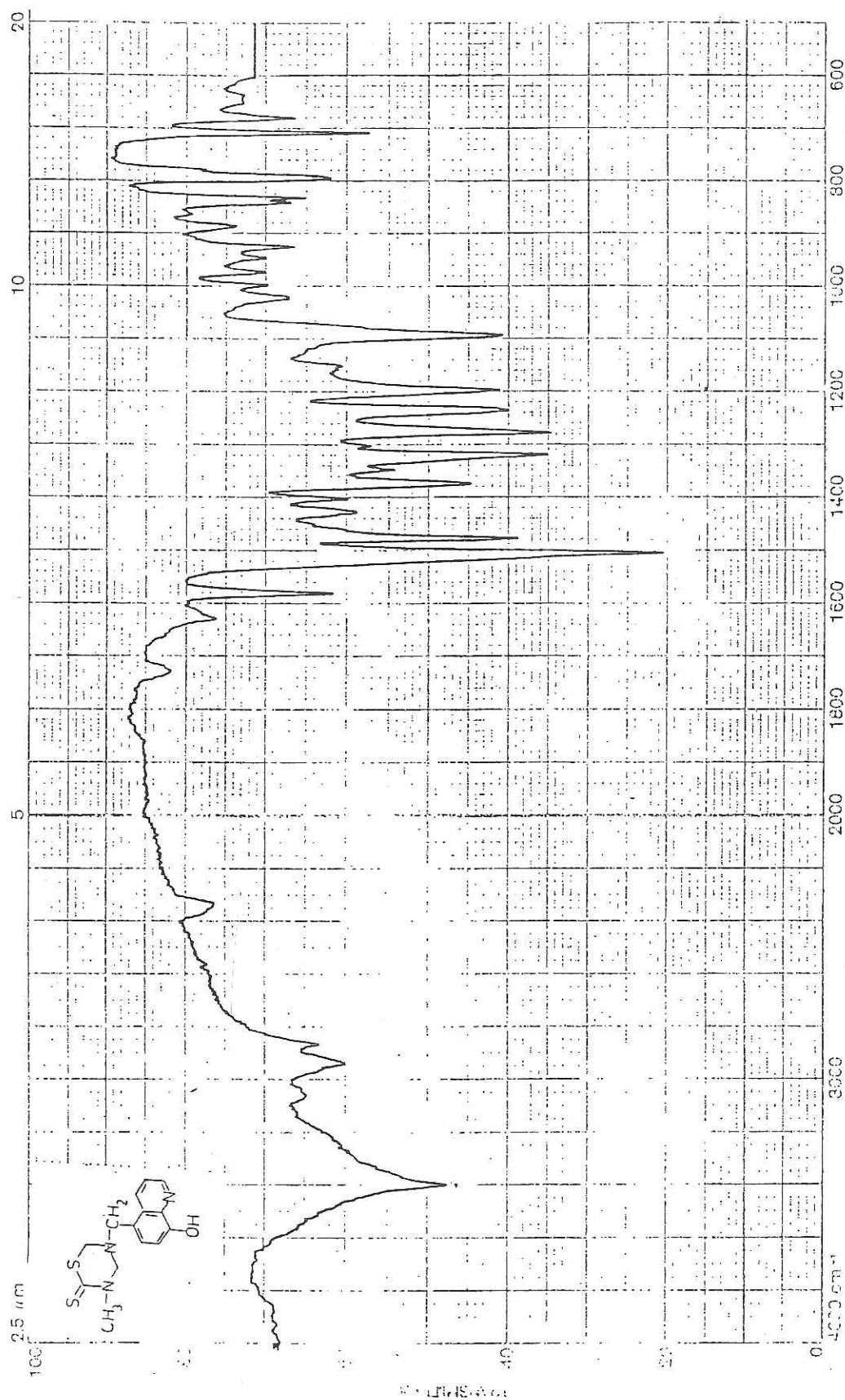


Figure 13. The IR Spectrum of 3-Methyl-5-(8-Hydroxy-5-Methyl Quinolin-2-ylthio)thiazine

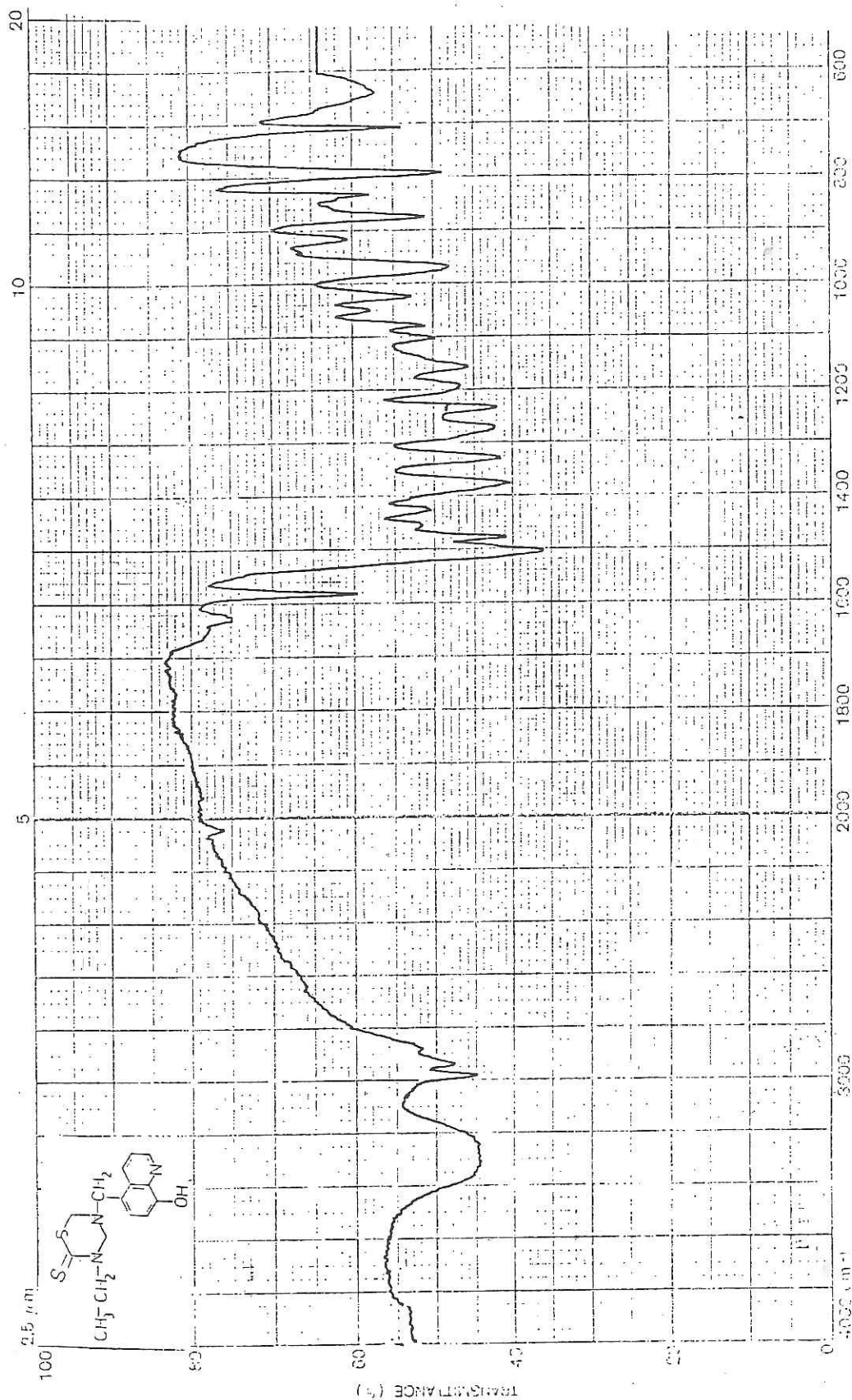


Figure 14. The IR Spectrum of 3-Ethyl-5-(8-Hydroxy-5-Methyl Quinolone)

Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

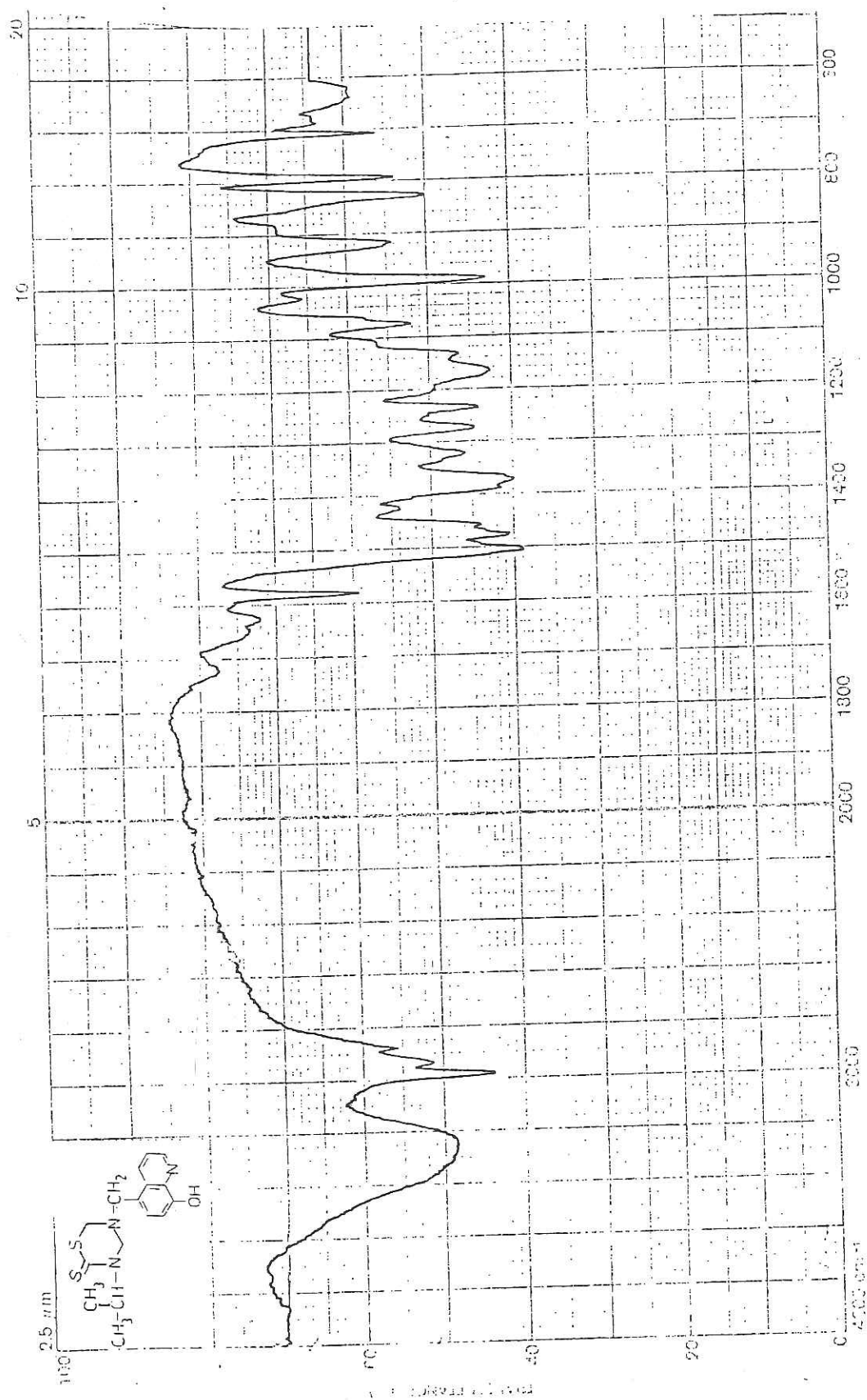


Figure 15. The IR Spectrum of 3-Isopropyl-5-(8-Hydroxy-5-Methyl Quinoline) Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione



Figure 16. The IR Spectrum of 3-n-Butyl-5-(8-Hydroxy-5-Methyl Quinoline) Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

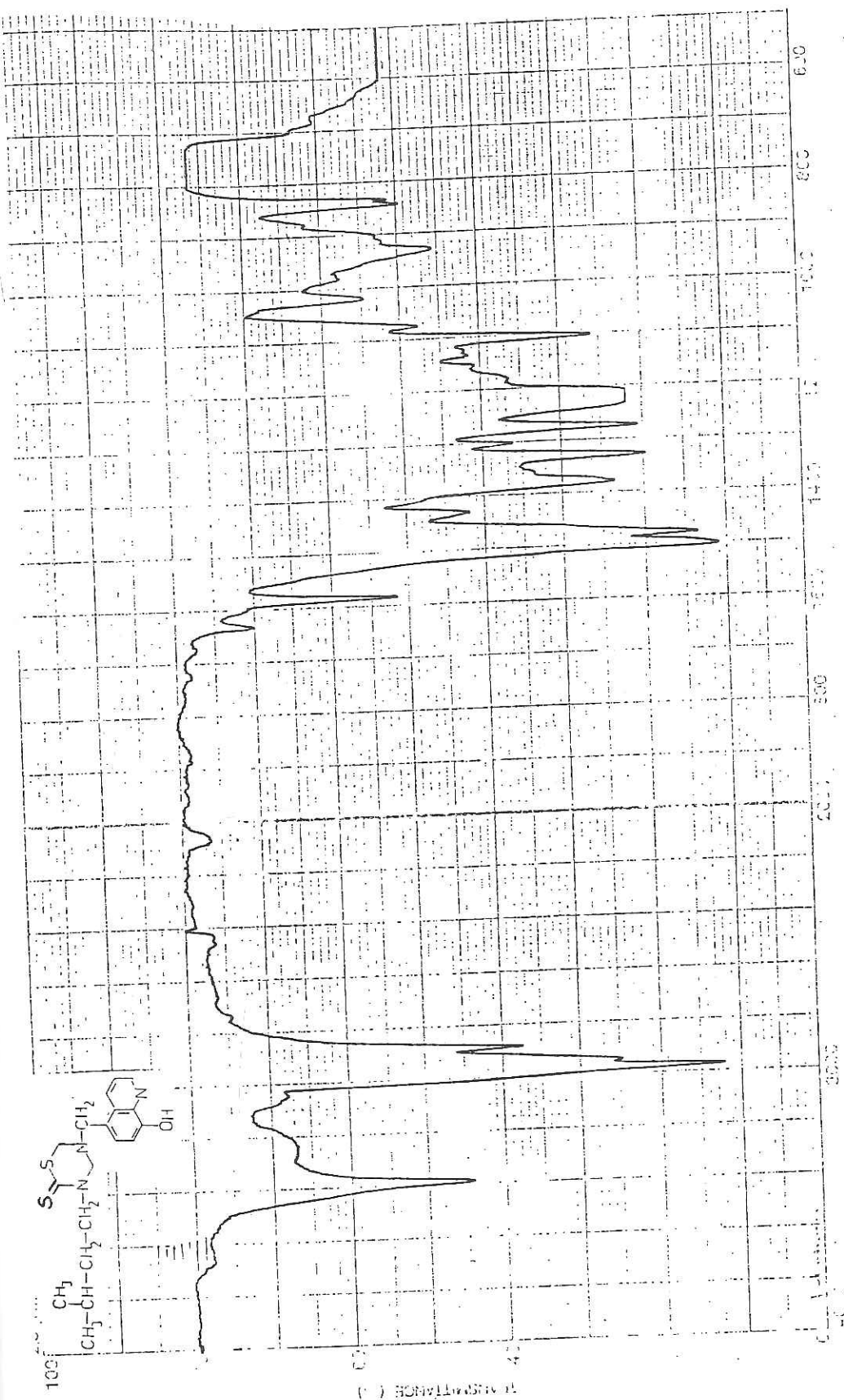


Figure 17. The IR Spectrum of 3-Isopentyl-5-(8-Hydroxy-5-Methyl Quinoline) Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione

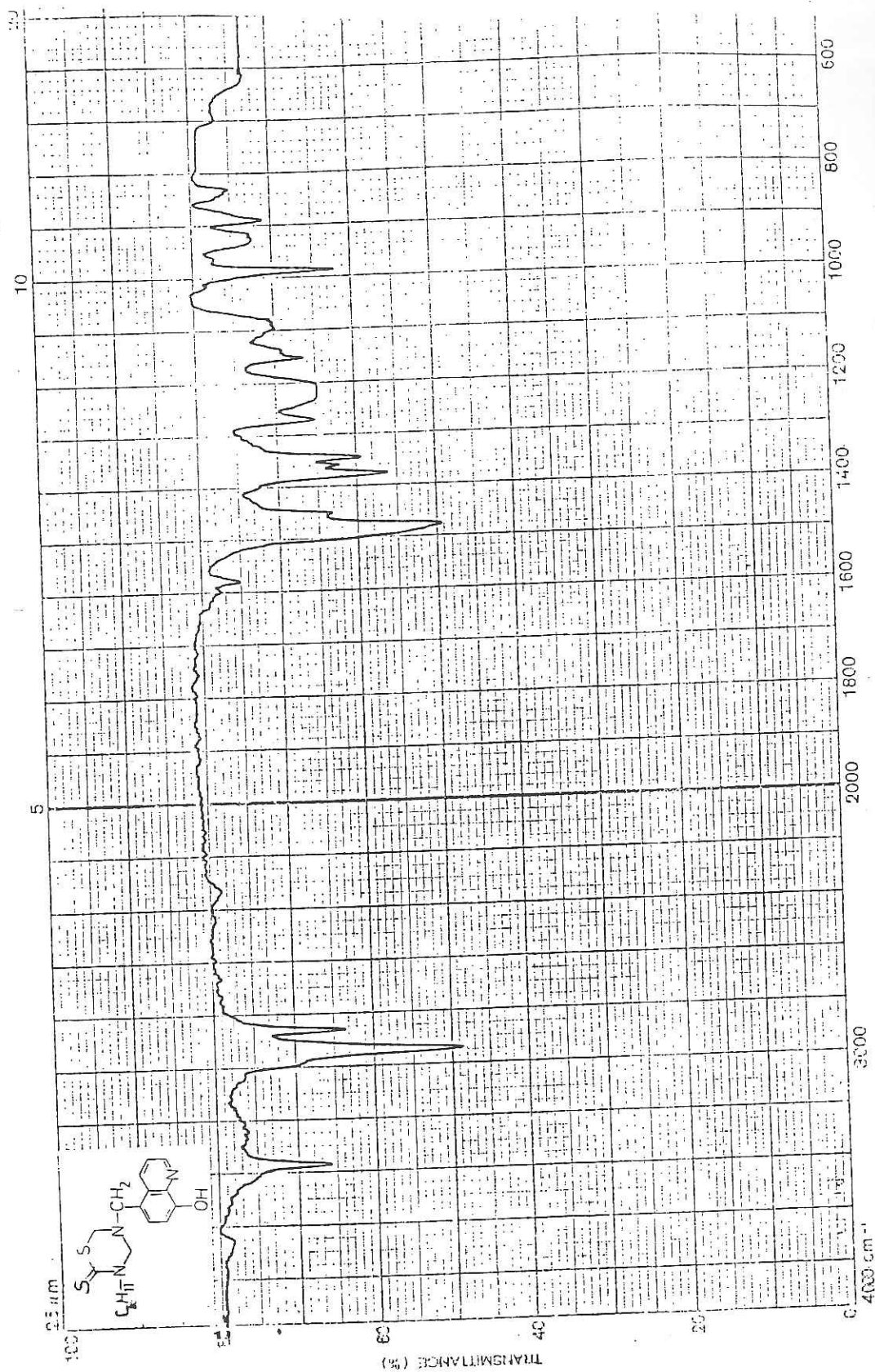


Figure 18. The IR Spectrum of 3-Cyclohexyl-5-(8-Hydroxy-5-Methyl
Quinoline) Tetrahydro-2H-1,3,5-Thiadiazine-2-Thione